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Cardiac complications of chronic, severe, refractory anemia with hemochromatosis

I. Acute pericarditis of unknown etiology

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ACUTE "nonspecific" pericarditis is a comparatively uncommon disease in children, though it has often been reported in adults since 1942. The condition, sometimes referred to as benign idiopathic pericarditis, does not fall into any specific etiological category. It has been suggested to be of viral origin, and recently there is increasing evidence that the Coxsackie group of viruses[1-4] and the influenza virus[5] may be responsible.

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CASE MATERIAL

This report deals with the development of acute pericarditis of unknown etiology in a group of 12 patients with Cooley's anemia (thalassemia major). The 12 patients affected were among 32 of similar age who have attended the transfusion clinic at New York Hospital. There were 6 males and 6 females. All had features on physical exam-

Table I

Patients	*Age at splenectomy (years)*	*Age at pericarditis (years)*	*Gross pericardial effusion*	*Pleural effusion*	*Heart failure during pericarditis*	*Age at death (years)*
I. C.	4	7, 23	+	+	0	—
S. S.	10	12	+	0	0	20
J. F.	1	13	+	0	0	19
J. N.	7	10, 11, 14, 15, 16	+	0	+	16
A. Di B.	15	17, 18, 24	0	0	+	—
A. V.	13	16, 18	0	+	0	—
F. G.	8	10, 11	0	0	0	13
P. C.	13	14	+	0	+	—
R. L.	—	12	0	0	+	12
M. G.	4	10	+	0	0	—
J. M.	—	10	+	0	0	—
A. C.	14	14, 14	+	+	0	—

ination and laboratory studies characteristic of Cooley's anemia and hemosiderosis. Splenectomy, as part of the treatment for Cooley's anemia, was performed on 10 of the 12 patients between the ages of 13 months and 15 years. The first episode of pericarditis developed within one month of operation in 2 patients, within the following year in 2, and in the others it occurred 3 to 10 years after splenectomy.

Attention was first called to the complication in these patients in 1955.[6] By the time of Smith's report[7] in 1957 on infections in children who have had splenectomies, this illness had occurred in 6 patients, one of them with 2 attacks and one with 3 attacks. Subsequently, an additional 6 have developed the condition, so there are now 12 patients who have had a total of 22 attacks of pericarditis.

The salient features to be described are summarized in Table I. Six patients had more than one attack, and one had 5 attacks between October, 1953, and February, 1960. Recurrences took place several months to several years after the previous episode. While the age at onset of the first bout of pericarditis varied from 7½ to 17 years, there was only one patient below the age of 10, and only 2 above the age of 15 years. The average age at the initial illness with pericarditis was 12 years. Except for one episode in 1942, all the attacks occurred during the period 1950 to 1960 and, again with a single exception, they occurred between the months of October and May. There was one attack in August, a recurrent episode which followed a tonsillectomy by 2 weeks. Fig. 1 shows the incidence by months of the year. On 4 occasions one patient developed pericarditis soon after another one had shown evidence of it. S. S. and J. F. (Cases 1 and 2, below) both had signs of pericarditis in the winter of 1950-1951, within a period of 5 weeks; J. N. and A. D. developed it simultaneously in October, 1953, and again in January and February, 1960; J. M. and M. G. were affected within a month of each other in the spring of 1959.

Presenting symptoms and signs. An antecedent upper respiratory infection varying in duration from 4 days to 2 weeks was present in 7 patients, and in 2 others there was a history suggestive of it. Three patients had diarrhea preceding the cardiac symptoms and one patient had a papulovesicular skin rash.

The symptom common to all patients in each attack was precordial chest pain, which was aggravated by inspiration and on lying down and was better tolerated in the upright position. Nine patients described pain referred to the shoulder and one, to the abdomen. Shortness of breath was noticed by 7 patients with accompanying cough in 3. Fever was present in 7 immediately preceding admission.

All showed physical findings characteristic of pericarditis, sometimes with effusion. Pericardial friction rub was noted in one or more attacks in the 12 patients. The rub was usually transient but in 3 patients it

persisted for over a month. Muffled heart sounds were present in 5 patients and gallop rhythm in 4. All had the systolic murmurs found in chronic anemia, and no change in these murmurs was noted during the attack of pericarditis.

During an attack in each of 8 patients, there was evidence of gross pericardial effusion by physical examination, x-rays, fluoroscopy, and electrocardiograms. Roentgen studies revealed increasing cardiac size with poor or absent pulsations (Figs. 2 and 3). Sometimes a double density of cardiac silhouette within a distended pericardial sac could be discerned (Fig. 2*B*). As the patients recovered, the cardiac silhouette decreased to the previous size (Fig. 3). Concomitant pleural effusion appeared in 3 cases in addition to the pericardial effusion.

The electrocardiogram showed changes typical of the development and evolution of pericarditis.[8, 9] Elevation of the S-T segments was noted in the limb leads but was often more striking in the left precordial leads. The T waves became low, diphasic, or negative, depending upon the stage of resolution of pericarditis. Decreased voltage of the electrocardiographic waves in comparison with previous tracings was found in the patients with effusion. The electrocardiographic changes were fleeting in nature in the patients with mild, brief attacks of pericarditis.

White blood cell counts were difficult to interpret because the total count was not always corrected for the large number of normoblasts characteristic of Cooley's anemia. As recorded, they varied between 9,000 and 36,000 per cubic millimeter. There was, however, a polymorphonuclear response, averaging 66 per cent and ranging from 41 to 81 per cent. Blood cultures taken on 8 patients did not grow out any organisms. Nose and throat cultures from all patients revealed normal flora. Virus studies were performed during the last 2 patients' attacks but to date no agent has been isolated. The heretophil antibody was elevated in one of the 5 patients in whom it was determined. On no occasion was a pericardial tap considered necessary to relieve tamponade, nor was it attempted as a diagnostic measure. The Mantoux test was negative.

Course. The duration of the illness varied from a few days to 5 months but was usually 2 to 3 weeks. Although several patients had a fever before coming to the hospital, there was remarkably little fever once they came under observation for the pericarditis. A moderate temperature elevation of a few days' duration was present in 7 of the patients during hospitalization. When the fever and substernal pain subsided, the patients generally appeared comfortable and did not look sick. Sometimes this signified the end of a mild attack of pericarditis, but in 8 instances in as many patients, the relief of pain coincided with the development of a gross pericardial effusion (Figs. 2 and 3). The discrepancy between the apparent comfort of the child and the radiologic and physical signs of steadily accumulating effusion was sometimes striking. Heart failure, not present previously, developed during the episode of pericarditis in 4 patients, 2 of whom had gross effusion at the time. Digitalization and rest in bed relieved their symptoms and peripheral edema; however, one child (R. L.) who went into heart failure coincidently with the onset of chest pain and signs of pericarditis died suddenly during the second week of his illness. Another (J. N.) died during the fifth attack of pericarditis, this time with effusion and heart failure. Although he became free of edema after 3 months of therapy for the failure, the cardiomegaly did not regress and

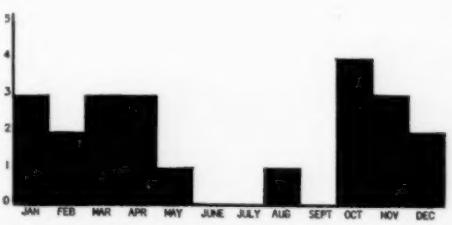
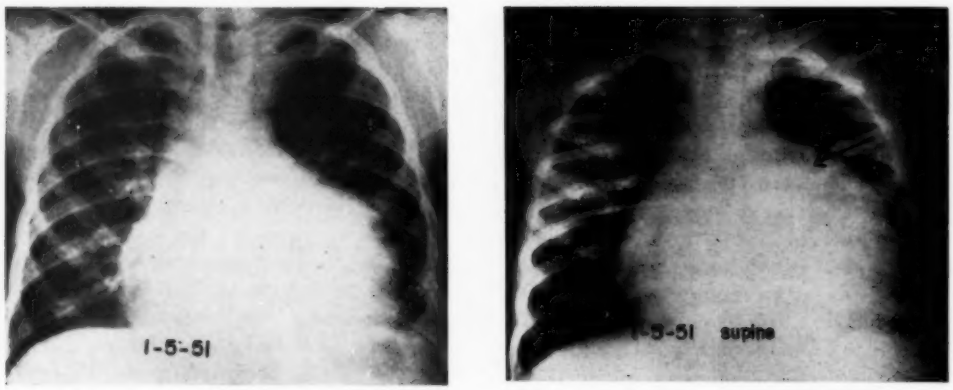


Fig. 1. Incidence of pericarditis according to months of the year. The number of cases is shown on the left. Except for one recurrent episode in August following a tonsillectomy, the attacks occurred between October and May.



A *B*

Fig. 2. Case 1, S. S., age 12 years. Note increased transverse diameter of cardiac silhouette due to pericardial effusion, and change in configuration as patient moves from upright position (*A*) to supine (*B*). Arrow indicates distended pericardial sac within which the cardiovascular shadow is visible.

the pericardial friction rub continued to be heard intermittently. He died 5 months after the onset of this last and most prolonged attack. Postmortem examination of these 2 boys was refused. The other patients returned to their previous status after subsidence of the pericarditis, whether this was the initial episode or a repeat attack.

Therapy. Treatment was symptomatic and consisted mainly of bed rest and transfusions as before for the anemia. Digitalis was administered to patients in congestive failure. Antibiotics such as penicillin, streptomycin, or tetracycline, alone or in combination, were given for single periods of 3 to 15 days to each of 8 patients without appreciable effect on the illness. Those who received no antibiotics ran a similar course. Hormone therapy was not used.

Follow-up. Three patients (S. S., J. F., and F. G.) have subsequently died in chronic heart failure, each with evidence of hemochromatosis, at 2, 6, and 9 years, respectively, following a bout of pericarditis. During the terminal cardiac complication in these 3, there was no evidence of acute or chronic pericarditis. The hemochromatosis, heart failure, and cardiac arrhythmias common to this group of patients with chronic, severe anemia form the basis of another report.[10, 11]

Illustrative cases. Cases 1 and 2 were the first 2 patients to develop this complication during the decade, 1950-1960. The second case followed the hospitalization of the first by 5 weeks.

Case 1. S. S., NYH 291 967; born April 30, 1938; pericarditis Dec. 25, 1950; died April 5, 1958. Pallor had been noted from the age of 10 months, and transfusions were administered regularly from the age of $2\frac{11}{12}$ years, when the patient was first referred to this hospital. Because of increasing requirements for transfusions from 1947 to 1949, splenectomy was performed on Dec. 1, 1949. Hemosiderosis was widespread in the spleen. Pigmentary changes in the skin, characteristic of hemosiderosis, had been present from earlier childhood. A systolic murmur and slight cardiac enlargement preceded the present illness.

Early in November, 1950, she had fever, cough, sore throat, and precordial pain aggravated by inspiration. Her private physician administered penicillin, and the symptoms gradually disappeared after a week. She was well until one month later, when she developed swollen lymph nodes for a period of 3 weeks. On Dec. 25, 1950, she noted the onset of anterior chest pain, more severe than previously and worse with inspiration. She was more comfortable when

sleeping on two pillows. The chest pain was intermittent over the next 4 days. When an elevation of temperature to 39.2° C. developed, and a diffuse papulovesicular eruption appeared, she came to the hospital.

On admission on Dec. 29, 1950, there was a loud pericardial friction rub, maximal over the sternum but audible all over the precordium. Heart tones were muffled and the systolic murmur was unchanged. X-rays showed the heart size had increased and were compatible with an effusion, though, on fluoroscopy, cardiac pulsations were still evident. The electrocardiogram showed low voltage and abnormal T waves. The white blood count, corrected for nucleated red cells, was 20,000 with 57 per cent mature polymorphonuclear cells and 9 per cent bands. The hemoglobin was 9.5 Gm. Tuberculin tests, cultures from blood and the nasopharynx, cold agglutinins, and febrile agglutinins were negative. The heterophil antibody titer was 1:56 on Jan. 9, 1951, and 1:28 1 week and 3 weeks later, respectively.

The temperature remained elevated at 38.5° C. for 2 weeks and gradually became lower over the next 2 weeks. She did not complain of chest pain after the second day in the hospital, and the rash was equally fleeting, but from the third to the fourteenth hospital days there was increasing pericardial effusion. On fluoroscopy, pulsations of the cardiac silhouette were absent, and the fluid could be seen to shift from the supine to the upright position (Fig. 2). A left-sided pleural effusion and then bilateral pleural effusions developed.

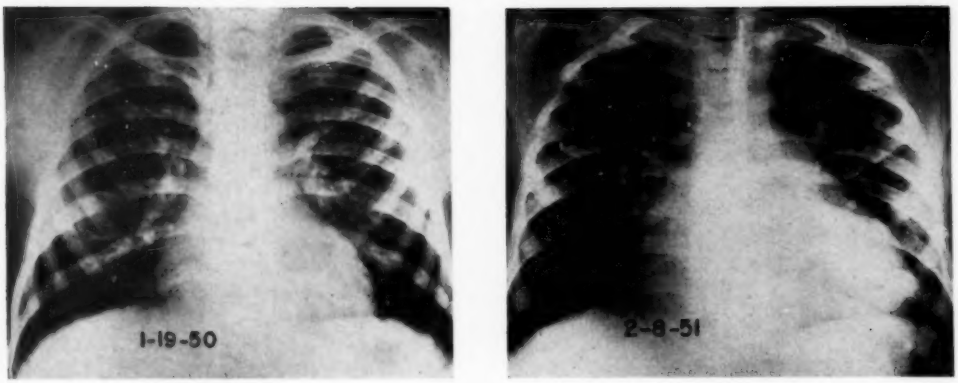
During this period a gallop rhythm and paradoxical pulse as well as Ewart's sign were demonstrable, and the venous pressure rose from 110 mm. saline on admission to as high as 315 mm. saline on Jan. 5, 1951. It remained elevated over 200 mm. for 2 weeks. The friction rub disappeared as the effusion increased but reappeared after a week and persisted for the next four weeks. She then became afebrile, the effusions cleared, the venous pressure dropped to 110-140 mm. saline, and the form of the T waves in the electrocardiogram improved. She was discharged after 2 months in the hospital.

Therapy, in addition to rest in bed and blood transfusions when the hemoglobin was below 7 Gm., consisted of penicillin for the first week and Aureomycin for the next 3 weeks. Neither agent had any apparent effect on the patient's course. Since she was not dyspneic and there were no râles in the lungs and no peripheral edema, she was not digitalized.

Following this attack of pericarditis, at age 12, the patient returned to her previous state of health, and there were no recurrences. After the age of 17, signs of hemochromatosis with progressive cardiac involvement became increasingly evident, and she died despite therapy for heart failure at the age of 20. Permission for postmortem examination was not granted.

Case 2. J. F., NYH 192 029; born Oct. 11, 1937; pericarditis Feb. 4, 1951; died Nov. 28, 1956. From the age of 3 months, the patient was under treatment at the New York Hospital for Cooley's anemia. Between 1938 and 1946, he was hospitalized 26 times for transfusions; on each occasion the hemoglobin level had decreased to 4 to 5 Gm. per cent. After 1946, transfusions every 2 weeks on an ambulatory basis maintained the hemoglobin above 7 to 8 Gm. per cent. Splenectomy was performed at the age of 13 months. Iron deposition in the spleen was slight. Skin changes of hemosiderosis developed a few years later. A systolic precordial murmur was present from infancy and, by the age of 7 years, cardiac enlargement and prolongation of atrioventricular conduction time were noted.

On his last visit to the clinic for transfusion prior to the present illness, he complained of a "runny nose" and diarrhea. Two weeks later, on Feb. 4, 1951, he was admitted to the hospital within 4 hours of the sudden onset of pain over the lower left chest. The next day the temperature rose to 38.5° C., a pericardial friction rub appeared, and the electrocardiogram showed elevation of the S-T segments.



A *B*

Fig. 3. Case 2, J. F., age 13 years. *A*, Last roentgenogram of chest prior to pericarditis, showing slight cardiac enlargement. *B*, Four days after onset of pericarditis showing increased cardiothoracic ratio due

The white blood cell count, corrected for nucleated red blood cells, was 34,000 per cubic millimeter with 56 per cent polymorphonuclear cells. The hemoglobin was 11 Gm. per cent, 2 weeks after a transfusion. Nasopharyngeal, blood, and stool cultures were negative for pathogenic bacteria; tests for cold agglutinins and febrile agglutinins were negative; and the tuberculin test was negative to 1.0 mg. of old tuberculin. The heterophil antibody titer was elevated to 1:448 when first determined 3 weeks after the onset; it rose to 1:896 3 weeks later.

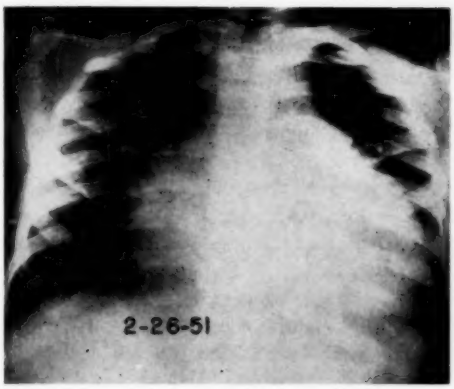
The temperature returned to near-normal levels after 3 days, and from the second week he was afebrile. The precordial pain disappeared after 2 days. However, a roentgenogram and fluoroscopic examination of the chest at that time showed evidence of pericardial effusion, which increased over the next 3 weeks (Fig. 3, *B* and *C*). The pericardial friction rub could be heard for a month, during which time the heart sounds were muffled. Ewart's sign over the left lower lung field could be demonstrated. For that month, electrocardiograms showed serial changes in the S-T segments and then in the T waves compatible with the evolution of acute pericarditis. The venous pressure measured around 200 mm. saline while the pericardial effusion was present; there were no symptoms or signs of cardiac tamponade or of congestive cardiac failure.

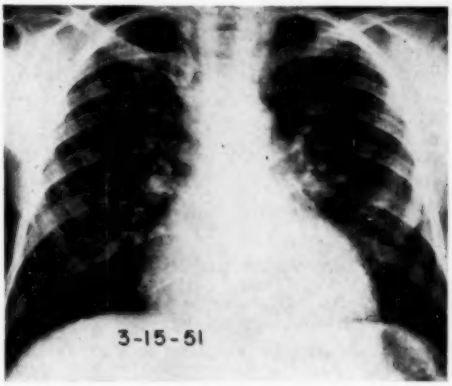
Except for rest in bed and transfusions when the hemoglobin dropped to 8 Gm. per cent, he received no specific therapy. After one month, the pericardial effusion resolved (Fig. 3, *D*), the friction rub disappeared, and the electrocardiogram returned to its previous form. He was discharged after 6 weeks in the hospital.

There were no recurrences of pericarditis during the next 5 years till the time of his death in refractory heart failure. The parents refused permission for postmortem examination.

DISCUSSION

In 1958 Bono and Garofalo[12] reviewed the literature and found 19 reported instances of acute benign pericarditis in childhood. They added one. Keith and associates[13] in their analysis of patients seen at the Hospital for Sick Children in Toronto over a period of 29 years found only 13 cases of nonspecific idiopathic pericarditis. The largest number observed by an author in a brief period was reported by Friedman and co-workers[14]: 6 cases occurred in Philadelphia during the year 1950 in patients between 3 and 12 years of age. During the 10 year period when our 12 patients were





C *D*

to some pericardial effusion. *C*, Greater pericardial effusion 18 days later. *D*, Resolution of pericarditis with effusion.

observed, there were only 3 other children hospitalized because of acute idiopathic pericarditis.

Although the etiology of the pericarditis is not known, there are several reasons for believing it to be an infectious condition with a predilection for this group of patients who, because of their basic disease, are unusually susceptible to infection. There is first its seasonal incidence coincident with the period of frequent respiratory infections. There was a single attack in the summer months, and that followed a tonsillectomy. Furthermore, the simultaneous development of acute pericarditis in more than one patient in the same clinic points toward a possible infectious etiology.

The clinical picture is similar to that of other reported cases of acute benign pericarditis and to the several reports of acute pericarditis due to the Coxsackie virus which have recently appeared in the literature. In 1957 Weinstein[1] reported acute benign pericarditis in a 25-year-old man with serologic evidence of infection with Coxsackie virus B, type 5. That same year Kagan and Bernkopf[2] recovered the Coxsackie virus group B, type 3, from the pericardial fluid and stools of a 10-month-old girl with pericarditis. When Gillett[3] in 1959 reported 4 cases of the syndrome and evidence that the causative agent may have been Coxsackie virus group B, type 5, he reviewed the previously described cases and found that there were 20 in which either a Coxsackie virus had been isolated or serologic evidence of infection with a Coxsackie virus had been shown. Null and Castle[4] soon added 4 more cases of pericarditis which occurred in an epidemic of Coxsackie virus group B, type 5, involving 17 patients. The influenza virus was implicated as a cause of acute "nonspecific" pericarditis by Adams,[5] who observed 8 patients during the influenza epidemic of 1957-1958. Type B virus was identified in 5 cases, both A and B in 2, and type A virus in 1 case.

The prevalence of acute pericarditis in patients with severe Cooley's anemia who have had splenectomies suggests that the removal of the spleen in some manner promotes increased susceptibility to this type of infection. While a causal relationship between splenectomy and predilection to severe and overwhelming infection has been controversial, data have accumulated supporting this relationship.[7, 15-18] It is also becoming increasingly apparent that the underlying hematologic condition for which splenectomy is undertaken plays a major role in the predisposition to infection.[19, 20] Divergent results obtained in assaying the antibody response to different types of agents in the splenectomized and nonsplenectomized

animals and human subjects may be due to the type of challenge employed.[19, 21, 22]

A possible etiological factor to be considered in our patients is hemosiderosis. Children with Cooley's anemia usually require frequent blood transfusions and they acquire hemosiderin deposits in most of their body tissues by the age of 5 to 7 years. At the time of the pericarditis all these patients showed the pigmentary changes of hemosiderosis in the skin, and there was evidence from biopsy of the liver and examination of the spleen at the time of splenectomy of widespread hemosiderosis and fibrosis of these organs. One can only speculate whether there was iron in the pericardium and, if so, whether the iron would render it susceptible to pericarditis; biopsy of the pericardium was not performed during the course of the illness in our patients, and postmortem examination was denied in the cases of those who died with signs of pericarditis (J. N., R. L.) or several years after the pericarditis (S. S., J. F., and F. G.).

There was no hemosiderosis of the pericardium in one child with sickle cell anemia and pericarditis who was studied at our hospital. This patient had received transfusions in the clinic from the age of 14 months because of a hemoglobin level of 5 to 6 Gm. Splenectomy was not performed. Acute, idiopathic pericarditis with effusion occurred in 1952 and did not recur. When he died 2½ years later at the age of 6 because of a cerebrovascular accident, the pericardial cavity was found to be obliterated by old, thin, fibrous adhesions. There was hemosiderosis of the spleen and liver but not of the pericardium.

That hemosiderosis of the pericardium is not causally related to the pericarditis is also suggested by the report from Boston of a 14-year-old patient with Cooley's anemia and recurrent acute pericarditis, similar to the cases herein described.[23] Biopsy of the pericardium during an exacerbation revealed thickening of the pericardium which appeared to result from serial episodes of involvement. Noteworthy was a relative lack of inflammatory cell infiltrate; scattered lymphoid or plasma cells were seen. No iron was demonstrable except in the pleura, which was lined by metaplastic serosal cells that contained iron. Material cultured at operation for bacteria and fungi showed no growth, and studies of the stool for virus were negative. The etiology of the pericarditis was not clarified, but it was suggested that this represented an instance of acute, recurrent benign pericarditis, possibly on a hypersensitivity basis, in a patient with thalassemia major and transfusional hemochromatosis.

The clinical course of these patients with Cooley's anemia is analogous to that of the postpericardiotomy syndrome following cardiac surgery[24] and to that reported following myocardial infarction.[25, 26] It is suggested that the common denominator in both these conditions in the initial episode is an inflammatory response to blood in the pericardium. There is no reason, however, to invoke this basis for the pericarditis just described since spontaneous hemorrhages into other parts of the body are not characteristic of Cooley's anemia.

Possibly the recurrences of pericarditis in the patients with Cooley's anemia and the others with acute, benign, viral, or nonspecific pericarditis as well as in the patients with postpericardiotomy and postmyocardial infarction syndromes represent a hypersensitivity phenomenon in a pericardium that has already responded to an initial insult, whatever the agent, with an inflammatory reaction. We have no evidence on this point.

SUMMARY

Twelve cases of children with Cooley's anemia who developed 22 attacks of acute pericarditis between 1950 and 1960 are reported. The average age at the time of their first attack was 12 years. In twenty episodes the pericarditis was a relatively benign, self-limiting condition, usually 2 to 4 weeks in duration, but in 2 patients it was part of the terminal illness. Just as in the condition, acute, benign, "nonspecific" pericarditis which these attacks resembled, the etiology of the pericarditis is unknown. It seemed

to be of infectious origin, but bacteriologic studies were unrevealing, and virus studies were not available in most of the attacks. The possible relationship to previous splenectomy and to hemosiderosis is discussed.

ADDENDUM

Patient I. C. has subsequently died suddenly at age 25 with a gastrointestinal hemorrhage. Prior to death she manifested electrocardiographic signs of cardiac involvement with hemochromatosis. Necropsy showed chronic adhesive pericarditis and interstitial fibrosis of the myocardium. Excessive iron deposition and fibrosis were present in the pericardium, myocardial fibers, and interstitial tissue of the heart, as well as in the liver, gonads, pancreas, etc.

Patient J. M., now aged 11, is recovering from a second attack of pericarditis with gross effusion, which began in November, 1960.

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Cardiac findings in idiopathic hypercalcemia of infancy

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IN 1932 Lightwood[1] described failure to thrive in a child who probably suffered from the syndrome subsequently named idiopathic hypercalcemia of infancy. The disease has been recognized with increasing frequency since that time.[2-33] The following features may be present: failure to thrive, elfin facies, mental retardation, renal impairment associated with urinary tract infection, generalized hypotonia, hyperactive deep tendon reflexes, facial paralysis, irritability, anorexia, vomiting, and hypercalcemia with normal phosphorus and normal or low alkaline phosphatase serum levels. In addition, cardiac murmurs and systemic hypertension are common findings. It is the purpose of this report to describe an additional patient with the classical features of idiopathic hypercalcemia of infancy who showed significant pathologic changes involving the cardiovascular system at necropsy. The clinical and pathologic findings in the cardiovascular system are summarized.†

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CASE REPORT

History of the present illness. A 19-month-old white Anglo-Saxon male was admitted to The Children's Hospital of Philadelphia because of vomiting and failure to thrive. At a prior admission at 2 months of age a low-pitched, systolic murmur was heard over the entire chest anteriorly and posteriorly, maximal in the third left intercostal space. The second pulmonic sound was normal, there were no thrills and no cardiomegaly, and the chest x-ray and electrocardiogram were normal. In addition to the cardiovascular findings, a mild right facial nerve paresis was noted. At 6 months of age the child was seen by a cardiologist who made a tentative diagnosis of ventricular septal defect. At 12 and 15 months of age, the character and location of the murmur were the same as previously described, but the second pulmonic sound was diminished, suggesting a diagnosis of pulmonary stenosis.

Past medical history. Pregnancy and immediate neonatal course were normal. Birth weight was 2,470 grams. The child was fed on an evaporated milk formula with a daily vitamin supplement containing 1,000 units vitamin D. From earliest infancy he was described as a poor feeder with frequent regurgitations. When solid foods were introduced at 6 months of age, regurgitation be-

came more prominent. By 13 months of age he was refusing all solids and consuming more than one quart of vitamin D enriched milk daily (400 U. vitamin D per quart). Weight gain was poor, so that at 19 months he weighed only 6,895 grams. Constipation was a prominent symptom. His general development was also slow. At the age of 19 months he could not sit without support and when held in a standing position he could not support his weight. He would continually rock while on his hands and knees but would not crawl nor had he spoken any words. He never seemed to respond to his mother's affection, never cuddled, nor played with a spoon or foods. During the 2 weeks prior to his admission all symptoms increased in severity. He was hospitalized because of an unexplained febrile illness.

Physical examination. The patient was small and chronically ill. He was very irritable, remained in a crouching position on hands and knees rocking front and back, and was generally unconcerned with people and objects around him. The temperature was 101.4° F., pulse 180 per minute, respirations 30 per minute and blood pressure 140/70 in the right arm. Body measurements were weight, 6,895 grams (average for a 5-month-old child); length, 70 cm. (average for an 8-month-old). His facies was elflike with prominent epicanthal folds, depressed nasal bridge, receding mandible, low set ears, and large overhanging upper lip. His hair was blonde and sparse. There were no teeth. A systolic murmur was audible over the entire precordium and was transmitted well to the back. It was loudest at the left sternal border in the third intercostal space, and was accompanied by a systolic thrill. The pulmonic and aortic second sounds were diminished. The skin was of normal color but had poor turgor and little subcutaneous fat. All peripheral pulses were normal. Neurological examination disclosed generalized hypotonia but active deep tendon reflexes. He sat poorly, and could not stand.

Laboratory data. Examination of the blood showed hemoglobin at 11.3 Gm. per 100 ml., and a white cell count of 18,050 with 43 per cent neutrophils and 57 per cent lymphocytes. Urinalysis revealed a pH of 5.0, a specific gravity of 1.008, and a trace of protein; the sediment contained 1 to 2 red blood cells and 15 to 20 white blood cells per high-power field. A catheterized urine culture yielded no growth at 5 days. Blood chemistry determinations included: carbon dioxide 16 mEq. per liter, sodium 154 mEq. per liter, chloride 113 mEq. per liter, potassium 4.2 mEq. per liter, fasting blood sugar 100 mg. per cent, nonprotein nitrogen 63 mg. per cent, total protein 7.0 mg. per 100 ml., albumin 3.6 Gm. per 100 ml., globulin 3.4 Gm. per 100 ml., calcium 12.5 mg. per cent, phosphorus 5.5 mg. per cent, alkaline phosphatase 1.9 Bodansky units, cholesterol 188 mg. per cent. Repeated urinalyses showed specific gravity of less than 1.013, proteinuria, and pyuria. Chest x-ray was normal. The bone age was commensurate with the chronological age. The electrocardiogram was within normal limits.

The findings of an elevated serum calcium

Fig. 1. J. P., aged 11 months.

Table I. Clinical and pathologic data which may have a bearing on the pathogenesis of the cardiac murmur in idiopathic hypercalcemia

Case No.	Author	Age (months)	Calcium (mg. %)	Heart		Kidneys	Blood pressure	Murmur
				Myocardium	Mitral, aortic valve			
11	Schlesinger, Butler, and Black[9]	35	13.3	Left ventricular hypertrophy	Degeneration, proliferation of intima, subendothelium of coronary artery	Nephrocalcinosis	150/95	No murmur
12		26	18.7	Focal calcification of subepicardial myocardium	Focal calcification of mitral valve	Nephrocalcinosis	170/80	Loud systolic
16	Morgan et al.[10]	12	14.8	Normal	Normal	Nephrocalcinosis	No data	No murmur
18	Rhaney and Mitchell[12]	10	14.5	Normal	Normal	Nephrocalcinosis	120/70	No murmur
19		8	16.3	Normal	Normal	Nephrocalcinosis	No data	No murmur
23	Dawson, Craig, and Perera[14]	11	16.4	Left ventricular hypertrophy	Normal	Nephrocalcinosis	150/60	Loud systolic
24	Lowe et al.[15]	10	15	Myocardial calcification	Normal	Nephrocalcinosis,	110/70	Soft systolic
31	Stapleton and Evans[16]	15	15.6	Calcification of myocardium and endocardium	Rigid and calcified atrioventricular valves	No data	Normal	Loud systolic
38	Joseph and Parrott[19]	23	13.3	Left ventricular hypertrophy, fibrous thickening of aorta	Thick mitral and tricuspid valve	Nephrocalcinosis glomerular atrophy	130	Loud systolic
50	Lightwood[1]	27	11	Calcification, degeneration	Normal	Nephrocalcinosis	180	Loud systolic
53	Present case	19	12.5	Left ventricular hypertrophy, right ventricular hypertrophy	Myxedematous degeneration of aortic valves, coronary subintimal proliferation	Nephrocalcinosis		Systolic murmur

level in association with other typical clinical signs confirmed the diagnosis of idiopathic hypercalcemia of infancy. Treatment was instituted with a low calcium, meat base formula and cortisone, 10 mg. three times daily. After some apparent clinical improvement, the child suddenly died on the thirteenth day of hospitalization.

Autopsy findings. Pathologic findings were limited to the heart. The parathyroids, thyroid, and other tissues were normal. The heart weighed 66 grams (54 grams normal for this age). Gross pathologic findings were limited to the ventricles and aortic valve. The right ventricle showed marked concentric hypertrophy and the wall measured 7 mm. in thickness. The left ventricle was hypertrophic and the wall measured 12 mm. in thickness. The aortic valves were rigid, yellowish, and firm in consistency.

On microscopic examination there was a moderate degree of myocardial hypertrophy. In the coronary arteries there was a marked degree of subintimal proliferation extending to the media and marked but eccentric thickening of the vessel walls. The proliferative process had the appearance of myxedematous connective tissues with an abundance of pale-staining eosinophilic ground substance. Periodic acid–Schiff stain showed a faintly positive reaction in these areas. The aortic valve showed a marked degree of myxedematous degeneration and a strongly positive reaction with a periodic acid–Schiff stain. Schujeninoff's technique was used for detection of calcium crystals in all sections, and no evidence of calcifications was found in the endocardium, myocardium, coronary arteries, valves, and aorta.

REVIEW OF LITERATURE

The clinical cardiovascular findings in 52 previously reported cases of idiopathic hypercalcemia of infancy and in our case were correlated. No murmurs were recorded in 11, and in 8 others no data were available; 33 patients had a significant heart murmur. All these were described as systolic and of at least Grade II intensity. Although a few were apical, most were maximal along the upper left sternal border. One of the murmurs was accompanied by a thrill. In one patient the murmur did not appear until 18 months after the diagnosis was established.[8] In several cases the murmur disappeared or lessened either spontaneously or after therapy. Significant hypertension, systolic pressure greater than 130, or diastolic pressure greater than 80 mm. Hg was observed in 15 cases. Electrocardiographic changes were demonstrated in 8 cases, primarily increased P and T wave voltage. Despite the hypercalcemia there was only one instance of a diminished Q-T interval. Only one patient had an abnormal x-ray of the chest.

The autopsy data on 11 patients are summarized in Table I. In 4 of these cases no murmur was noted, and in 3 of these 4 no cardiovascular lesions were found. Of the remaining patients with murmurs, 5 had

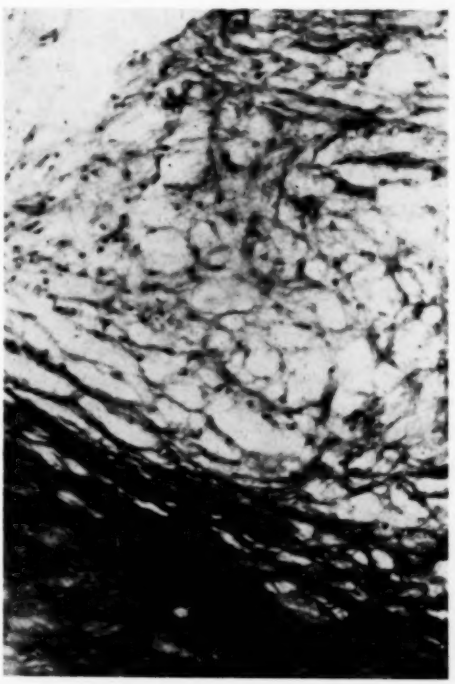

Fig. 2. Section through the aortic valve showing the generalized myxedematous changes. (Original magnification ×400.)

pathologic changes involving the valves, 4 had myocardial calcification, 4 had ventricular hypertrophy, and 2 had coronary artery changes.

DISCUSSION

The pathogenesis of the heart murmur in idiopathic hypercalcemia is obscure. Concomitant anemia is usually mild and in at least one reported case the murmur persisted even though the anemia was corrected.[29] Congenital cardiac anomalies have not been found at necropsy in any infants with idiopathic hypercalcemia. Other conditions with hypercalcemia, viz., sarcoidosis, multiple myeloma, hyperparathyroidism, and bone neoplasms, are rarely associated with significant heart murmurs. However, the pathologic findings associated with hypercalcemia secondary to vitamin D intoxication are strikingly similar to those reported here. Excessive vitamin D administration to rats results in myxedematous changes in the heart valves.[30] Ross[34] reported 4 instances of vitamin D intoxication in infants. Postmortem examination of one of them revealed extensive calcification of the right ventricle, the left atrium, and the coronary and renal arteries. Debre[35] described calcareous deposits in the myocardium and kidney, and 2 instances of hypertension in patients with vitamin D overdosage. Although these patients were children, the authors did not consider them to have the idiopathic hypercalcemia syndrome, but ascribed the changes to vitamin D poisoning. There should be no question regarding diagnosis in 2 adult patients who received massive doses of vitamin D, each for approximately one year prior to death. At autopsy both showed extensive cardiac, renal, and arterial calcification.[36, 37] These similarities in cardiovascular findings in vitamin D intoxication and in idiopathic hypercalcemia would suggest that a defect in the metabolism of vitamin D or of related substances with vitamin D activity may be the underlying factor in the pathogenesis of idiopathic hypercalcemia of infancy.[7] Moreover, the changes in the cardiac valves described in these patients are the most likely causes of the murmurs heard in this syndrome. The origin of the hypertension which is often present in this syndrome has not been established. The frequent occurrence of impaired renal function and the finding of nephrocalcinosis at autopsy suggest that renal factors may be relevant.

Because many of the clinical manifestations may be reversible with adequate therapy, it is of considerable importance that the diagnosis be made as early as possible. Any infant with an elfin facies, who fails to thrive, and who has hypertension or a murmur which is hard to classify, should be investigated for idiopathic hypercalcemia of infancy.

SUMMARY

1. A case of idiopathic hypercalcemia of infancy is presented and 53 cases previously reported are reviewed, with emphasis on the cardiovascular findings.

2. The cardiovascular findings in this patient at necropsy and in 10 additional cases are summarized.

3. A significant heart murmur was found in 63 per cent and hypertension in 43 per cent of the cases reviewed.

4. Correlation of the clinical and pathologic observations suggests that the murmurs are due to pathologic changes involving the valves and myocardium.

5. The importance of considering the diagnosis of idiopathic hypercalcemia of infancy in a child who fails to thrive and who has hypertension and/or a cardiac murmur is stressed.

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Experimental observations on cardiac arrhythmia during exchange transfusion in rabbits

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ALTHOUGH exchange transfusion has become a simple and familiar treatment for hemolytic disease of the newborn, the definite mortality risk which it carries is often overlooked. Walker and Mollison[1] reported that 22 per cent of 550 deaths from hemolytic disease of the newborn occurred during or within 4 hours of exchange transfusion. They did not comment on the possible cause of the deaths.

Various authors[2-5] have described the electrolyte disturbances which follow exchange transfusion with citrated blood. These disturbances produce specific electrocardiographic changes.[6-8] In addition there have been a few case reports of gross cardiac arrhythmia, ventricular fibrillation, and cardiac arrest.[5, 8-11] A review of these cases suggested that a cause of the symptoms might be found in alterations in the composition of donor blood such as the addition of citrate, the lowering of ionized calcium and pH, the elevation of plasma potassium by prolonged storage, and the inadequate warming of refrigerated blood.

There is seldom a safe opportunity to study the effect of such factors in the production of cardiac arrhythmia in the human infant. As an alternative, experimental exchange transfusions were performed on rabbits, simulating the transfusion of infants as nearly as possible. The purpose of these experiments was: (1) to compare citrated blood with heparinized blood, by observation of the electrocardiographic changes; (2) to observe the changes produced by donor blood of high plasma potassium content; (3) to observe the changes produced by chilling of the donor blood; and (4) to observe the effect of intravenous injection of calcium on cardiac arrhythmias which arise during exchange transfusion.

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METHOD

The rabbits were healthy white adults of both sexes, weighing between 2 and 5 kilograms. The larger animals were used as donors, the smaller as recipients.

The donor blood was drawn from a cannula, inserted into the right carotid artery under ether anesthetic. An average of 116 ml. was obtained from 55 donor rabbits. It was collected in silicone-coated bottles containing the anticoagulant solution, either citrate or heparin. The citrate anticoagulant was the standard Red Cross Blood Bank mixture of dextrose 1.76 Gm., sodium citrate 1.58 Gm., and anhydrous citric acid 0.528 Gm. in 120 ml. of distilled water; 2.5 parts of donor blood were added to 1 part of citrate anticoagulant. Heparinized donor blood was prepared by the addition of donor blood to 20 mg. of heparin powder (Connaught Laboratories) dissolved in 10 ml. of isotonic saline. The blood was stored at 4° C. for 24 hours before the exchange transfusion.

Hyperpotassemic blood was prepared by adding potassium chloride solution (2 mEq. per milliliter) to the donor blood a few minutes before the exchange transfusion, the volume of solution added being sufficient to raise the plasma potassium concentration in the donor blood to 25 mEq. per liter. The concentration of a sample of the mixture was measured immediately before the exchange transfusion began. During the exchange transfusion the donor blood was either maintained at room temperature (average, 21° C.), or cooled to 1° C. in an ice bath.

The recipient animals were anesthetized by the intraperitoneal injection of 1 Gm. of Urethane per kilogram of body weight. The external jugular vein was exposed by dissection, and a polyethylene catheter of 3 mm. internal diameter inserted into the vein until the blood flowed freely. In some of the animals examined post mortem, the point of the catheter lay just above the level of the right auricle. A uniform rate of exchange transfusion was maintained by the withdrawal followed by the injection of 10 ml. of blood within a period of one minute. Samples from each withdrawal of blood were taken for measurement of the serum potassium and calcium concentrations.

Standard Lead II tracings were obtained on a direct writing Sanborn electrocardiograph at the end of each injection of 10 ml. of donor blood. The rectal temperature of the recipient animal was measured before and periodically during the exchange transfusion by a standard mercury thermometer. Serum and plasma potassium concentrations were determined by the method of Hawk, Oser, and Somerson.[12]

Definition of the end points of each experiment. Each transfusion was continued until the donor blood had all been injected or the animal died. The "end points" were usually preceded by a variety of alterations in the ECG patterns. There were three basic patterns:

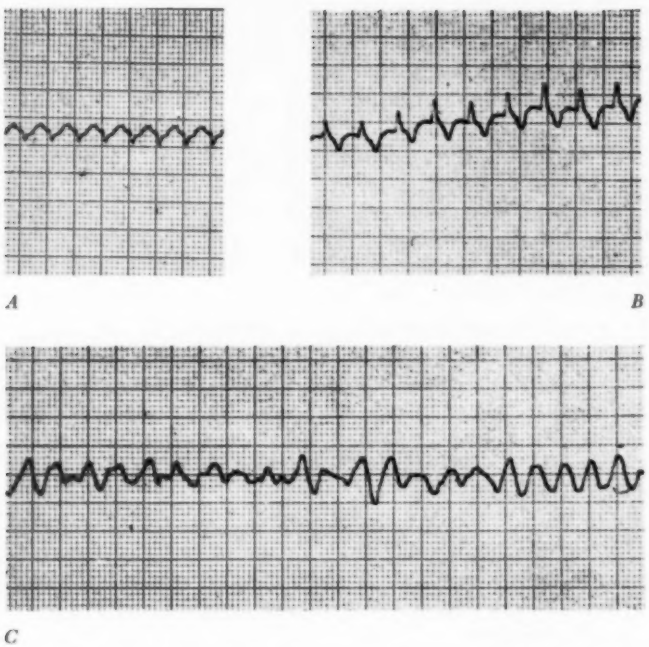
1. The normal, in which the normal appearances of the tracing recorded before the exchange transfusion were preserved throughout, and in which the heart rate did not decrease to less than half the value at rest.

2. Ventricular fibrillation. A typically irregular tracing is illustrated in Fig. 1. The occurrence of ventricular fibrillation was regarded as a fatal outcome to the exchange transfusion, since, without resuscitation, very few animals survived more than a few minutes.

3. Gross cardiac arrhythmia. This was defined as any alteration in cardiac rhythm (other than ventricular fibrillation) severe enough to slow the heart to less than half the normal rate or to impair the animal's general condition. The adverse effects were cyanosis, dyspnea, apnea, and the accumulation of excessive frothy secretions in the pharynx. A typical pattern of gross arrhythmia is illustrated in Fig. 2. Such patterns were occasionally followed by the death of the animal within a few minutes.

RESULTS

Death during exchange transfusion (Table I). Exchange transfusion was performed on 57 rabbits. Ten were transfused with normo-



A *B*

C

Fig. 1. Exchange transfusion with citrated hyperpotassemic blood at 20° C. *A*, Before exchange transfusion (Lead II). *B*, After exchange of 60 ml. *C*, Ventricular fibrillation after exchange of 75 ml.

potassemic citrated donor blood, 19 with hyperpotassemic citrated blood, 13 with normopotassemic heparinized blood, and 15 with hyperpotassemic heparinized blood. The highest mortality occurred in the group of rabbits transfused with hyperpotassemic citrated blood. Fifteen of the 19 rabbits in this group died. There were 2 deaths among the 15 rabbits transfused with hyperpotassemic heparinized blood, 1 among the 10 rabbits transfused with normopotassemic citrated blood, and none in the 13 rabbits transfused with normopotassemic heparinized blood.

Where citrated blood was used, the volume exchanged was on the average greater, because the dilution of the blood with citrate solution was greater than the dilution with heparin.

Electrocardiographic patterns during exchange transfusion (Table II, Figs. 1 and 2). Twelve of the 19 rabbits transfused with hyperpotassemic citrated blood developed ventricular fibrillation. All 12 died. Ventricular fibrillation did not develop in any of the other experimental groups. The fibrillation was always preceded by prolongation of Q-T_c interval and, with only two exceptions, by depression of the S-T segment and increased amplitude of the T wave.

The onset of ventricular fibrillation was not closely related to the level of serum potassium in the recipient rabbit. The average serum potassium in 56 healthy donor rabbits was 3.4 mEq. per liter (range 1.8 to 6.0 mEq. per liter); the average serum potassium in blood samples taken immediately before the onset of ventricular fibrillation was 10 mEq. per liter (range 6.5 to 17.8 mEq. per liter). Five of the 15 rabbits given hyperpotassemic heparinized blood were found to have serum potassium levels above 10 mEq. per liter (range 13.4 to 17.7 mEq. per liter), but none developed ventricular fibrillation.

The electrocardiographic patterns of gross

cardiac arrhythmia varied considerably. The only consistent feature was alteration in cardiac conduction. Specific patterns could not be correlated with the type of donor blood used. Six of the 15 rabbits with gross cardiac arrhythmia died.

Response to injections of calcium glucoheptonate (Table III). The first 6 rabbits transfused with hyperpotassemic citrated blood developed convulsions after the injection of 20 to 30 ml. of donor blood. The injection of 0.5 ml. of 10 per cent calcium glucoheptonate relieved the convulsions, and also corrected cardiac arrhythmia if this had developed. The calcium injection was repeated after each recurrence of the convulsions. In the next 5 rabbits transfused with hyperpotassemic citrated blood, 0.5 to 1.0 ml. of 10 per cent calcium glucoheptonate was injected prior to the start of the exchange, and this was repeated after the injection of every 30 ml. of donor blood. Although the injection of calcium did not prevent the final onset of ventricular fibrillation, the volume of donor blood which the recipient rabbit could tolerate was increased in direct proportion to the volume of calcium injected. Two rabbits which did not receive calcium developed ventricular fibrillation following the injection of 20 ml. of donor blood. All these experiments were conducted with hyperpotassemic citrated donor blood at 21° C.

The effect of chilling the donor blood. Ten rabbits received transfusions of citrated blood chilled to 1° C., and 12 of chilled heparinized blood. The most frequent electrocardiographic changes were lengthening of the P-R and Q-T_e intervals, S-T segment deviation, and elevation of the T wave. The

Table I. Deaths during exchange transfusion

	Temp. of donor blood	*No. of rabbits*	*Deaths*	*Average volume of donor* blood injected (ml./kg.)*
Citrated donor blood				
Potassium normal	21° C.	6	1	88
	1° C.	4	0	76
Potassium > 17.0 mEq./L.	21° C.	13	10	38
	1° C.	6	5	102
Heparinized donor blood				
Potassium normal	21° C.	4	0	62
	1° C.	9	0	62
Potassium > 17.0 mEq./L.	21° C.	12	1	78
	1° C.	3	1	40

*This represents the average volume of donor blood injected before (a) the onset of gross cardiac arrhythmia or ventricular fibrillation or (b) the end of the exchange transfusion.

Table II. Electrocardiographic abnormalities during exchange transfusion

	Temp. of donor blood	*ECG abnormalities*		
		None	*Arrhythmia*	*Fibrillation*
Citrated donor blood				
Potassium normal	21° C.	5	1	0
	1° C.	3	1	0
Potassium > 17.0 mEq./L.	21° C.	2	3	8
	1° C.	2	0	4
Heparinized donor blood				
Potassium normal	21° C.	3	1	0
	1° C.	6	3	0
Potassium > 17.0 mEq./L.	21° C.	9	3	0
	1° C.	0	3	0

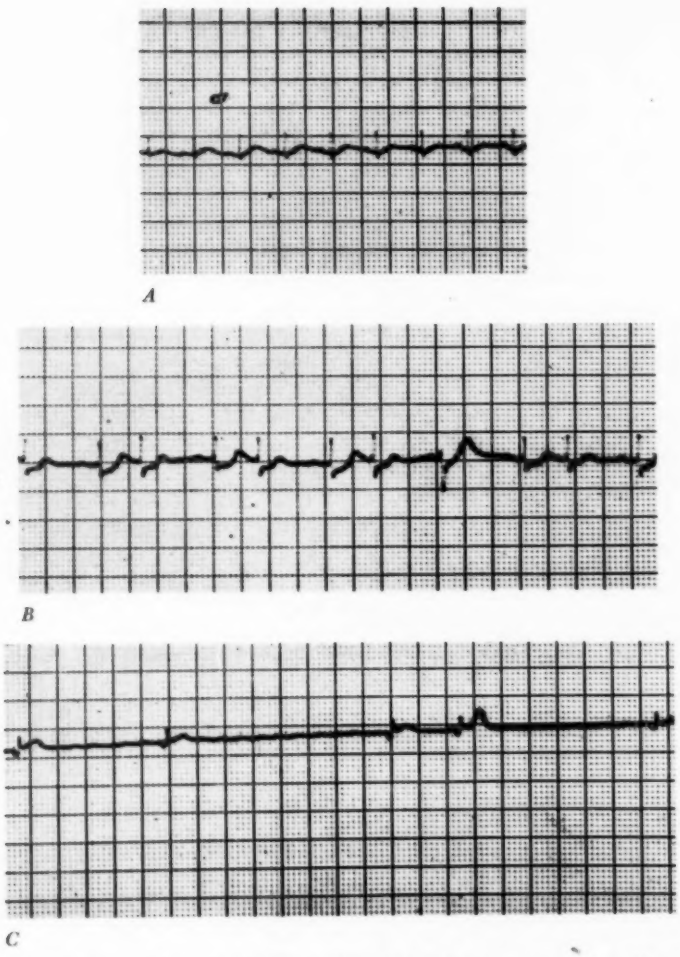


Fig. 2. Exchange transfusion with heparinized blood plus ethylenediaminetetra-acetic acid at 1° C. *A*, Before exchange transfusion (Lead II). *B*, Coupled beats after exchange of 100 ml. *C*, Gross arrhythmia after exchange of 120 ml.

incidence of ventricular fibrillation and gross cardiac arrhythmia and the mortality rate were unaltered.

Six rabbits transfused with hyperpotassemic citrated blood at 1° C. tolerated an average donor volume of 102 ml. per kilogram. The 13 rabbits transfused with hyperpotassemic citrated blood at 20° C. tolerated an average volume of 38 ml. per kilogram.

DISCUSSION

The most significant finding in these experiments was the high incidence of ventricular fibrillation during exchange transfusion with hyperpotassemic citrated donor blood. The electrocardiographic changes which preceded the onset of ventricular fibrillation were similar to those described by Ludbrook and Wynn,[13] Hubbard and associates,[14] and Argent[15] in citrate intoxication associated with blood transfusion in man. Furman and his co-workers[6] reported prolongation of the Q-T_e interval in 2 infants undergoing exchange transfusion with citrated blood. Joos[8] demonstrated prolongation of the R-ST and Q-T_e intervals with

occasional elevation of the T wave in infants given exchange transfusions of citrated donor blood, the potassium content of which was between 5.5 and 18.6 mEq. per liter. Taylor[11] reported ventricular fibrillation in a newborn infant following exchange transfusion with hyperpotassemic citrated blood, the fibrillation in this case being preceded by prolongation of the Q-T_e interval, and slight depression of the S-T segment. Bolande and collaborators[5] reported cardiac arrest and death of infants during exchange transfusion with hyperpotassemic citrated donor blood, but no electrocardiograms were made.

When the toxic effects reported in these accounts are compared with those in the rabbit experiments, the sequence of events seems very similar. Prolongation of the Q-T_e interval, S-T depression, and increased amplitude of T waves precede the onset of ventricular fibrillation; ventricular fibrillation precedes cardiac arrest. In the infant, cardiac arrest has probably followed this sequence in the majority of cases. A major hazard to the infant in exchange transfusion, therefore, is citrated blood of high potassium content.

The other findings in these experiments, though of less significance, are of some practical value. The increased tolerance of the rabbit heart to hyperpotassemic citrated blood after the prophylactic injection of calcium shows how important it is to administer calcium when exchange transfusion is performed. In the rabbit, electrocardiographic prolongation of the Q-T_e interval always preceded, and depression of the S-T segment with increased amplitude of the T wave usually preceded the onset of ventricular fibrillation. These early electrocardiographic changes were reversed by the administration of calcium. In infants in whom exchange transfusion may have to be performed with old stored blood of high potassium content, electrocardiographic monitoring and injection of calcium at the first sign of electrocardiographic abnormality could prevent deaths. The dose of calcium glucoheptonate which produced arrest of the rabbit heart was at least five times the volume required to correct early electrocardiographic changes.

The observations on chilled donor blood suggest that it did not play any significant part as a cause of death or cardiac arrhythmia in the rabbit. Although it is desirable to warm refrigerated blood to body temperature before exchange transfusion in humans, the time lost may be dangerous to an infant who has severe hemolytic disease. Some reassurance may be gained from the fact that the rabbit has a greater tolerance for hyperpotassemic blood at 1° C. than at 20° C.

SUMMARY

There have been a number of reports of cardiac arrhythmia during exchange transfusion in infants suffering from hemolytic disease. Exchange transfusion was performed in rabbits, simulating human transfusion as closely as possible. The electrocardiographic changes were followed to compare citrated with heparinized blood. The effects of raising the potassium content and lowering the temperature of the donor blood were also observed.

Exchange transfusion with hyperpotassemic citrated blood was fatal to 15 of 19 rabbits. Twelve of the 15 deaths resulted from ventricular fibrillation. Ventricular fibrillation did not occur in rabbits given citrated blood of normal potassium content or heparinized blood. The onset of ventricular fibrillation was delayed by the prophylactic injection of calcium gluconate. When

Table III. Increased tolerance to citrated hyperpotassemic donor blood following the injection of calcium glucoheptonate

Volume of 10% calcium glucoheptonate	*No. of rabbits*	*Average volume of donor* blood injected (ml./kg.)*
0	2	20
0.1-1	5	41
1.1-2	3	59
2.1-3	2	67
3.1-4	1	78

*This represents the average volume of donor blood injected before (a) the onset of gross cardiac arrhythmia or ventricular fibrillation or (b) the end of the exchange transfusion.

the temperature of the donor blood was lowered there were recognizable electrocardiographic changes, but they were not associated with an increased incidence of ventricular fibrillation or a higher mortality.

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Immunologic and thyroid function studies in euthyroid children with goiter

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BETWEEN January, 1955, and January, 1960, 31 clinically euthyroid children were referred to the Endocrine Clinic of The Children's Hospital of Philadelphia because of a goiter. Except in one child with a nodular gland, the thyroid enlargement was diffuse and there was no associated cervical adenopathy to suggest the likelihood of carcinoma. The patients lived in greater Philadelphia, an area in which iodine deficiency goiter is extremely rare, and none was known to have ingested goitrogenic foods or drugs. Many of the patients had been referred with the diagnosis of adolescent goiter.

In order to establish the cause of the thyroid enlargement, these children were studied both by the standard tests of thyroid function and by recently devised immunologic techniques to detect the presence in the serum of antibodies which react with human thyroid extracts. In some, the serum was also studied for abnormal protein patterns, and in a few patients an open biopsy of the thyroid was performed. The results of these studies, summarized herein, suggest that in this locality goiters in euthyroid children are most commonly associated with an autoimmune process directed against the thyroid gland.

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METHODS

Serum protein-bound iodine (PBI) was measured by the method of Barker, modified by Grossman and Grossman.[1] Serum butanol-extractable iodine (BEI) was determined as follows: after butanol extraction by the procedure of Pickering and Kontaxis,[2] 130 mg. iodine-free bovine albumin and sodium carbonate were added to the extract, which was dried in a vacuum oven; incineration and colorimetry were carried out as in the PBI method, and simultaneously with specimens for PBI. I^{131} uptakes were measured with a scintillation counter 24 hours after administration of 1 to 7 μc of the isotope. In some patients, the uptake was repeated after the intramuscular injection of 2.5 units of

thyrotropin (TSH) every 12 hours for a total of 4 doses.

Initially, serum thyroid-agglutinating antibodies were assayed by a semiquantitative technique. Subsequently the method of Witebsky[3] was employed, modified in two particulars: (1) the tanned, human Group O, Rh-negative erythrocytes were incubated with the antigen, thyroid extract, at 37° C. for 15 minutes; (2) the reaction between the coated cells and test serum was allowed to take place at room temperature for 3 to 4 hours in a 1:50 dilution of buffered pooled human plasma. Thyroid complement-fixing antibodies in serum were detected by the method of Roitt and Doniach.[4] The thymol turbidity of serum was measured by the method of Reinhold and colleagues[5]; the cephalin-cholesterol flocculation, by the method of Hanger[6]; total serum protein, by the method of Reinhold.[7]

RESULTS

Patient material and thyroid function tests. As recorded in Table I the patients ranged in age from 1 to 17 years, but most were prepubertal or in early adolescence. Only 4 of the 31 were males. Although all were clinically euthyroid, in many some abnormality of the organically bound iodine in serum was found. In 12, the PBI exceeded 8.5 μg per cent. In the 21 studied by both the PBI and BEI methods, the ratio PBI:BEI exceeded the normal range in 7. Seventeen of the 31 patients showed some abnormality by one or both of these indices of thyroid function. In contrast, the results of the I^{131} uptakes were quite variable. Six of the 20 patients were found to have a subnormal uptake at 24 hours, 5 showed a slightly elevated uptake. The uptake could not be correlated with the PBI or BEI in many instances. Thus Subject 11 was found to have the highest PBI and the lowest I^{131} uptake. A possible disturbance in the fixation of iodide in the thyroid was sought for in cases Nos. 2 to 5, 23, and 29 by administering potassium thiocyanate during the study, but none was found. In 7 patients the I^{131} uptake was repeated after injection of TSH. In the 4 subjects with initially normal uptakes an adequate response to TSH was found; in the 3 with previously elevated uptakes, no response was evident. This suggested that in the latter the thyroid was already maximally stimulated by endogenous TSH and could not respond further.

Thyroid antibody studies. The serum of all 31 patients was examined for the presence of agglutinins specific for human thyroglobulin. As recorded in Table I, antibodies of this type were detected in 21 patients. The complement-fixation test, used to measure antibodies to intracellular thyroproteins rather than to thyroglobulin, was performed in 27 instances and was positive in 14. With the two assays combined, thyroid antibodies were detected in the serum of 27 of the 31 patients. In contrast, 55 sera obtained from Philadelphia Serum Exchange donors with no history of thyroid disorder were assayed for thyroid agglutinins and complement-fixing antibodies and proved to be negative. Sera from 3 adults with chronic thyroiditis, proved by biopsy, served as positive controls and were positive by both tests.

Serum protein studies. Ten of the 31 patients were studied by the methods listed in Table II. It will be noted that the thymol turbidity tests were usually normal, but the results of the cephalin-cholesterol flocculation test were abnormal in 6 of the 9 sera tested. This correlated well with an elevation of gamma-globulin concentration, noted in all but 1 of the 7 sera examined by paper electrophoresis. In direct contrast, the concentration of beta globulin was frequently subnormal and exceeded the normal range in only 2 instances.

Thyroid biopsies. An open biopsy of the goiter was performed in 5 of the patients listed in Table I. Cases 6 and 8 were found to have diffuse follicular hyperplasia without inflammatory changes. The remaining 3 specimens were described by the pathologist, Dr. William Yakovac, as follows:

Case 2. "The follicles are small in size with a poor colloid content. The epithelium varies from cuboidal to columnar. There is occasional papillary infolding of the epi-

Table I. Immunologic and thyroid function studies

No.	Initials	Age (Years)	Sex	PBI	PBI/BEI	Radioactive iodine uptake		Antibody titers	
						Initial	Post-thyrotropin	Agglutinins	Complement-fixing antibodies
1	K. P.	6	F	7.4	1.0	—	—	1+*	8
2	P. D.	6	F	8.3	3.5	46	46	1+*	—
3	R. S.	9	F	7.7	1.5	53	46	2+*	—
4	V. M.	6	M	5.2	—	27	—	2+*	—
5	B. S.	9	F	6.1	—	12	—	1+*	0
6	J. A.	1	F	7.6	1.0	31	—	1+*	0
7	A. H.	16	F	6.7	1.2	54	55	2+*	0
8	E. S.	2	M	9.9	1.1	54	—	1+*	0
9	J. H.	8	F	7.0	1.4	—	—	1+*	0
10	O. C.	7	F	8.1	1.0	32	58	35	0
11	P. C.	7	F	12.5	—	3.4	—	78,125	512
12	M. L.	11	F	6.3	1.3	25	—	0	0
13	E. K.	8	M	7.8	2.3	23	—	0	8
14	R. K.	10	F	5.2	1.3	43	69	15,625	0
15	D. D.	10	F	7.4	1.0	—	—	0	0
16	B. P.	12	F	7.9	2.6	—	—	0	256
17	M. B.	15	F	9.0	1.5	16	—	0	0
18	A. S.	10	F	10.2	—	6	—	78,125	512
19	C. S.	9	F	9.7	1.4	23	—	0	4
20	G. C.	9	F	8.0	1.6	—	—	5	64
21	L. F.	17	F	5.8	1.4	—	—	25	16
22	S. H.	14	F	9.8	—	—	—	15,625	1,024
23	T. B.	12	M	7.4	2.9	32	45	78,125	256
24	S. B.	10	F	9.1	2.9	46	—	3,125	64
25	M. G.	13	F	8.6	—	—	—	0	16
26	S. C.	8	F	10.6	2.9	15	—	625	256
27	P. R.	7	F	5.2	—	—	—	625	0
28	C. B.	5	F	9.2	—	26	57	625	0
29	C. M.	17	F	10.4	—	13	—	78,125	0
30	J. S.	11	F	5.4	2.0	—	—	0	1,024
31	H. G.	9	F	10.1	—	—	—	0	—
Normal				5.0 to 8.0	1.0 to 1.5	20 to 45		0	0

*These tests were performed at a serum dilution of 1:2 by observing gross clumping of red cells. Positive reactions were graded 1+ to 4+. Subsequent studies demonstrated that 1+ or 2+ by the semiquantitative method was equivalent to a titer varying from 5 to 3,125 by the modified method of Witebsky.[8]

Table II. Serum protein studies

Case	Thymol turbidity (Maclagan units)	Cephalin-cholesterol flocculation	Total protein (Gm. %)	Gamma globulin (Gm. %)	Beta globulin (Gm. %)
2	4.9	+	7.0	1.3	0.5
3	—	0	7.5	1.12	0.61
5	1.5	+++	—	—	—
8	1.3	0	—	—	—
11	2.9	++++	8.2	1.66	1.12
13	4.3	++	6.4	1.24	0.98
14	1.4	+++	—	—	—
18	2.9	+++	7.0	1.39	0.69
23	3.2	++	6.6	1.2	0.3
28	3.5	-	7.1	1.3	1.5
Normal (Age 3-13)	1 to 4	0 to +	5.5 to 7.2	0.89 to 1.18	0.72 to 1.08

thelium. The stroma shows a moderate increase in fibrous tissue. It is also infiltrated with lymphocytes to a marked degree. Some germinal centers are clearly seen in the lymphocytic infiltrate. Some macrophages can be identified in and out of the follicles and plasmocytes are abundant in the stroma."

Case 4. "The follicles are irregular in shape and filled with colloid. Many follicles have ruptured and there are giant cells present in the stroma showing evidence of colloidophagy. The interstitial tissue is increased and there are numerous chronic inflammatory cells (mostly lymphocytes) infiltrating along connective tissue planes."

Case 30. "The acini are for the most part small, with little colloid. The lining epithelium is high cuboidal to columnar. The cytoplasm of the lining cells is clear and at times lightly basophilic. There is a moderate infiltration of lymphocytes in the stroma with, in places, formation of germinal centers. Also seen are a few macrophages, present in the lumen of some acini, and plasmocytes in the stroma."

DISCUSSION

The most striking and consistent abnormal laboratory finding in this group of 31 children with goiters was the presence of antibodies to human thyroid extracts in the serum of all but 4 patients. Recent immunologic studies help to explain the significance of this finding. Witebsky and Rose[8] produced antibodies to rabbit thyroid by injecting thyroid extracts into rabbits, and at the same time produced in these animals a form of thyroiditis which histologically resembles lymphocytic thyroiditis in man. This experiment led Roitt and associates[9] to study patients with lymphadenoid goiter, and they were able to demonstrate antibodies to human thyroid extracts in the serum of such patients. These investigators interpreted this to mean that thyroid protein, which normally does not escape the gland, if released into the circulation acts as a foreign protein and provokes an immunologic response in the body. The antibodies formed in this way return to damage the thyroid gland, producing a form of thyroiditis. While antibodies can be detected in the serum of patients with many different types of thyroid disease, high titers are found almost exclusively in patients with thyrotoxicosis, spontaneous myxedema, and lymphocytic thyroiditis.[10]

Since 87 per cent of the children with unexplained goiters in this series had antibodies in their serum and were clinically euthyroid, it might seem reasonable to assume that most of them had thyroiditis. The abnormalities of protein-bound iodine in serum, in more than half the cases, particularly the elevated PBI:BEI ratio, are of the type previously reported in thyroiditis.[11] The positive thymol turbidity and cephalin-flocculation tests and the abnormal serum protein patterns found by paper electrophoresis, measured in fewer patients, have been found with about the same frequency in other reported cases of thyroiditis.[12-14] The goiter in each patient gradually regressed in response to treatment with desiccated thyroid, lending further support to this diagnosis.

Unfortunately, none of the available tests is specific for thyroiditis, the diagnosis of which can only be made histologically. Moreover, the clinician is reluctant to advise an open biopsy of the thyroid gland in a young girl with a small goiter and no enlargement of the cervical lymph nodes to suggest the presence of thyroid malignancy. In this series an open biopsy was considered warranted in only 5 patients, all of whom had antibodies in their serum. The biopsy confirmed the suspected diagnosis of thyroiditis in 3 patients. In 2 it did not; rather it disclosed diffuse follicular hyperplasia. It could be argued that the latter represented a very early phase of thyroiditis, and that inflammatory changes would have been detected in some other area of the gland; but it seems equally likely that the serum antibodies in these 2 patients indicated only that some nonspecific insult to the thyroid gland had occurred, which did not produce thyroiditis, or that thyroid hyperplasia itself,

of whatever etiology, can lead to the production of antibodies. These 2 biopsied cases emphasize the diagnostic limitations of the available immunologic tests.

The detection of thyroid antibodies in the serum of most of these children with unexplained goiters can, therefore, be taken as proof only of the presence of an autoimmune process involving the thyroid gland, not of thyroiditis. While this is true, the present study also suggests that the presence of thyroid antibodies, together with other abnormal but less specific thyroid function and serum-protein tests, and regression of the goiter in response to thyroid treatment are strong presumptive evidence for the diagnosis of thyroiditis. If the results of the very small number of biopsies performed in this series can be considered representative of what would be found in others, it seems justified to conclude that in this locality most, but not all, euthyroid children with a goiter have a form of chronic thyroiditis.

SUMMARY

Thirty-one clinically euthyroid children with goiters were studied by immunologic and other laboratory procedures. The results of these studies indicate that most of the goiters were associated with an autoimmune process directed against the thyroid gland. The diagnosis of thyroiditis was confirmed by open biopsy in 3 patients. In 2 patients with thyroid antibodies in the serum, the biopsy revealed follicular hyperplasia without inflammatory changes, emphasizing the diagnostic limitations of the available immunologic tests. However, high titers of antibodies in euthyroid children with goiters, when associated with abnormalities of thyroid function tests, abnormal serum-protein patterns, and regression of the goiter in response to treatment with desiccated thyroid, are strongly suggestive of the presence of a form of chronic thyroiditis.

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Peritoneal drainage of subdural hematomas in infants

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MODERN concepts in the treatment of subdural hematomas in infants date from the 1932 report of Peet and Kahn[6] who treated 9 cases with excision of the membranes. The normal mental development of the surviving patients was in striking contrast to that of the previously reported series treated without membrane removal.[8] Following modification of the surgical method by Ingraham and Heyl[4] and Ingraham and Matson,[5] there has been wide acceptance of the necessity for membrane removal.[1, 2, 3]

The generally accepted treatment has been gradual decompression of the subdural space by needle aspiration followed by craniotomy and excision of the membranes. This technique has been successful in our hands but the occasional case of recurrent subdural fluid collections with increased intracranial pressure following membrane removal led to the use of internal drainage of the fluid. Biopsies of the recurrent membranes, reminiscent of the thin membranes found occasionally at primary excision, led later to the utilization of internal drainage as a primary form of treatment in a series of infants with liquefied subdural hematomas. The operative technique, the results of therapy, and the pathologic changes in serial biopsies of the membranes are summarized in this report.

The procedure used was subdural peritoneal drainage. The operative technique consisted of placing the child partly on his side, making a posterior parietal trephine opening over the collection of fluid and a left transverse lower quadrant abdominal incision. Teflon or silicon rubber tubing was tunneled subcutaneously between the incisions. Two tubes were used for bilateral drainage and separately tunneled from the scalp incisions to the neck and then tunneled together to the abdominal incision. Multiple openings were made in both ends of the tubing, 5 to 6 cm. of which was placed into the subdural space and attached firmly to the pericranium. The lower end of the tubing was placed in the left lateral peritoneal gutter and firmly attached to the external oblique fascia. In our early procedures, the tubing was left in place for 8 to 10 weeks but in the later cases the time interval was shortened to 4 to 5 weeks. The tubing was removed by opening the trephine incision and pulling the tubing from the

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abdomen. Another trephine opening was then made to check the subdural space and to obtain another membrane biopsy.

The results of subdural peritoneal drainage are summarized in Table I. The causes for failure of the procedure are listed in Table II. There were 14 patients in the series, 4 of whom had reaccumulation of subdural fluid collections following craniotomy. These 4 were treated with repeated subdural aspiration followed by internal drainage. Two of the 4 patients had bilateral collections; 2, unilateral. Only one side failed to clear with internal drainage and re-excision of membranes was done. Decompression by subdural aspiration was done in the remaining 10 patients until their clinical condition improved and the subdural fluid was clearing of blood (usually 8 to 10 days). Parietal trephines with membrane biopsy and external drainage for 24 to 48 hours was then done. Only one side cleared with this therapy. After establishing the failure of external drainage by subdural aspiration, internal drainage was then carried out. There were 7 bilateral and 3 unilateral collections in the 10 patients. Nine sides cleared with internal drainage, 8 sides failed to be adequately drained. The failures were treated by craniotomy and excision of the membranes with good results.

There were 2 deaths. One child died of septicemia following dehiscence of a thoracic wound which had been used as an aid in tunneling the tubing subcutaneously. The dehiscence appeared related to the wound and underlying tubing being positioned over a rib. No further incisions were made over areas of bony prominence and no other such difficulty was encountered. A 3 day delay in the family's returning the child to the hospital following the dehiscence allowed infection of the wound and dissemination of the infection. The child died 7 days after readmission.

The second death in this series was of a child who was doing well following subdural peritoneal drainage but whose family, either through fear or ignorance, did not return for follow-up care and the child died 4 months after drainage with large bilateral collections of subdural fluid and with the drainage tubing curled up in each subdural space. Following this incident, both ends of the tubing were attached with sutures to surrounding tissue at the time of insertion to avoid migration of the tubing.

Biopsies of the membranes were made both before and at various intervals after drainage. It was hoped that some correlation between membrane thickness and success or failure of internal drainage would clarify the indications for or against membrane excision. It was, however, difficult to be certain of exact membrane thickness both because there were differences in thickness at different areas of the membrane and also because, technically, the pathologic specimens were not satisfactory for width measurements. There was, neverthless, some correlation with duration of symptoms and failure of internal drainage in that, in the children with less than a 6 week history, there were only 4 failures in 12 sides, while in the children with longer than a 6 week history there was 4 failures in 5 sides. In the recurrent subdural collections following craniotomy, all of which were less than 7 weeks after craniotomy, there was one failure in 6 sides. This would indicate that with increasing duration of symptoms and, therefore, membrane maturity, internal drainage is less likely to be successful.

Table I. Internal drainage of subdural hematomas in infants

14 patients	23 sides
9 bilateral	
5 unilateral	
Success	14 sides
Failure (2 deaths)	9 sides

Table II. Causes of failure in drainage of subdural hematomas in infants

Blocked shunt	4 sides
Abdominal end 3	
Subdural end 1	
Loculation of subdural hematoma	1 side
Infection (died)	2 sides
Refused second stage (died)	2 sides

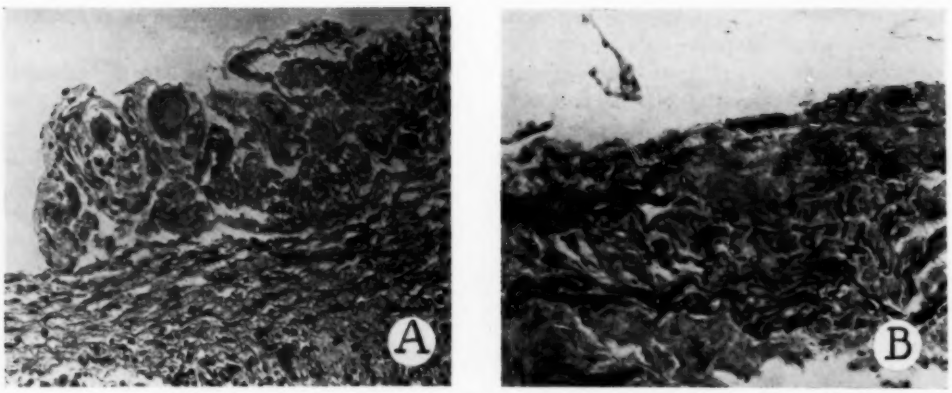

Fig. 1. *A*, Biopsy of predrainage subdural membrane showing cellularity, fibroblastic changes, and marked vascularity.

B, Biopsy of same membrane 12 weeks after internal drainage. Included in specimen is dura. There is marked regression of all the predrainage characteristics.

Although the membrane biopsies were not helpful in determining the parameters indicating membrane excision, the serial sections showed striking histologic changes correlating with the adequacy or inadequacy of the drainage. Fig. 1, *A* is a representative section of predrainage membrane biopsy demonstrating fibroblastic proliferation, vascularity, and reactive cellularity. Fig. 1, *B* shows the same membrane biopsied 12 weeks after drainage, showing marked decrease in vascularity and cellularity and with maturing fibroblastic change in apposition to the dura. In one case, re-exploration of the subdural space one year after drainage failed to reveal any signs of residual membrane. In contrast to this, inadequately drained membranes showed increasing vascularity, cellularity, and fibroblastic proliferation.

It is obvious even from this small series that internal drainage of subdural hematomas in infants is not a substitute for excision of membranes but rather an aid in the treatment of these children. It has the advantage of being a simple temporizing technique which allows a child in poor nutritional condition or other physical difficulties to be followed without frequent subdural aspiration. During this observation period, cure of the hematoma may be accomplished, saving the child from the more extensive operative procedure of craniotomy and excision of the membrane.

The membrane biopsy findings and the clinical course of the patients support the conclusions of Ransohoff[7] and Shulman and Ransohoff[9] that retained subdural membranes are not in themselves a cause of future central nervous system difficulty. The findings showed not only regression in the membrane when drainage was adequate but macroscopic disappearance of the membrane in one case within one year. The converse finding of increasing cellularity, vascularity, and fibroblastic proliferation in the membranes which were inadequately drained suggests that these characteristics are not inherent in the membrane but are the reaction of the membrane to persistent fluid collection of high protein content. However, only continued observation of these children over extended periods and comparison of morbidity, mortality, and mentation will give a critical evaluation of this type of therapy. It remains to be demonstrated that there are no other indications necessitating surgical removal of subdural membranes. At present the evidence appears clearly to indicate that the presence of a membrane is not in itself an indication for excision by craniotomy.

SUMMARY

A technique for internal drainage of subdural hematomas in infants is described. The results of subdural peritoneal drainage in 14 patients are summarized. There were 9 bilateral and 5 unilateral subdural hematomas in the group of infants. Good results were obtained in 14 of the 23 sides. Serial biopsy of the subdural membranes showed marked regression in membrane thickness, cellularity, and vascularity provided drainage was adequate. The results suggest that with adequate drainage of subdural hematomas in infants, excision of the membranes is not always indicated.

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Cation exchange resin therapy for hyperkalemia in infants and children

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THE dangers accompanying marked increases in extracellular potassium concentration are generally recognized. Regardless of etiology, removal of excess extracellular potassium may constitute an important, but difficult, therapeutic problem.

Early trials with rectal administration of cation exchange resins yielded results which were not as predictable in lowering serum potassium concentrations as were those following their oral administration.[1-3] Recently a cation exchange resin prepared in the sodium phase, sodium polystyrene sulfonate, (Kayexalate†) has been introduced. Since preliminary investigations seemed promising,[2, 4-7] a clinical evaluation of this drug was attempted in children.

It is the purpose of this report to review briefly the existing literature on the clinical use of exchange resins and to present 3 cases in the pediatric age range in which the above-mentioned resin was employed.

CASE HISTORIES

Case 1. B. B. (St. C. H. C. No. 591350), an $8\frac{8}{12}$-year-old white female was transferred to St. Christopher's Hospital for Children on March 24, 1959, in a semicomatose condition. From available records kept by her parents, retardation of growth had been present for at least 7 years. Anemia was noted 9 months prior to the present hospital admission. Uremia and hypertension were noted in another hospital during the week prior to her transfer to us.

Physical examination revealed extreme pallor and moderate dehydration. She responded only to painful stimuli. The patient's height was 44 inches and her weight was 36 pounds. Blood pressure was 160/40 in each arm.

The laboratory data are presented in Table I. Because of the hyperkalemia she received a retention enema of Kayexalate, 30 Gm. A second retention enema of 30 Gm. of Kayexalate was ordered the following day when the serum potassium concentration was 6.1 mEq. per liter. Inadvertently, the enema was not administered until the third hospital day. Hypokalemia resulted (K^+ = 2.8 mEq. per liter). Administration of supplementary potassium corrected this problem.

In view of the diagnosis of acute renal failure superimposed on some form of chronic renal disease, fluid intake was rigidly restricted. Small transfusions of blood and antihypertensive agents were administered. The patient became considerably more re-

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†*Manufactured by Winthrop Laboratories, 1450 Broadway, New York 18, N. Y.*

sponsive on the third and fourth hospital days, but then developed generalized convulsive seizures, bronchopneumonia, and congestive heart failure. Death occurred on April 1, 1959. Autopsy revealed a congenitally hypoplastic left kidney. The histologic changes in the right kidney were difficult to interpret but were considered to represent chronic glomerulonephritis.

Case 2. J. H. (St. C. H. C. No. 564635), a 2½-year-old Negro male, was admitted to St. Christopher's Hospital for Children on Feb. 14, 1959, because of generalized convulsive seizures that had lasted 3 hours. Blindness and right hemiplegia had been present for 6 months, following a convulsive seizure.

On admission he was noted to be in a state of postictal depression. There was some evidence of pneumonitis which was thought to have been due to aspiration. Convulsive seizures recurred intermittently over the next 3 days. He became progressively incapable of handling secretions and required a tracheotomy on the fourth hospital day. Pneumothorax developed requiring pleural drainage.

Oliguria was noted on the third hospital day. Repeated urinalyses revealed protein and red blood cells; eventually the specific gravity became "fixed" at 1.010. Hyperkalemia and severe metabolic acidosis with marked anion retention were present.

In view of a serum potassium concentration of 9.1 mEq. per liter (Table II), two retention enemas of Kayexalate (30 Gm. each) were administered during the evening of Feb. 18, 1959. Electrocardiograms

Table I. Laboratory data from Case 1*

Date		*3-24-59*	*3-25-59*	*3-26-59*	*3-27-59*	*3-28-59*	*3-30-59*	*3-31-59*
K^+	mEq./L.	6.9	6.1	4.1		2.8	3.4	4.0
Na^+		133	130	134		133	134	128
Cl^-		95	88	92	98	84	81	74
Co_2		6	7	9	18	13	13	12
BUN	mg. %	262	250	219		268	242	
Ca^{++}		7.4						
PO_4		9.5						
pH		7.11	7.14	7.15		7.29	7.22	7.11
Hemoglobin (Gm. %)		4.1	6.0	7.6	11.6		8.4	6.8
			↑ † †		↑ †			
Condition		Semi-coma		Alert; Bronchopneumonia		Melena Hematemesis	Semi-coma Convulsions	Death

*Note that 30 Gm. of Kayexalate was administered by high retention enema during the evening of March 24, 1959, and again on March 26, 1959. This second exchange resin enema seemed to be related to the subsequent hypokalemia noted on March 28, 1959.

†Blood transfusion.

↑ Cation exchange resin by enema.

Table II. Laboratory data from Case 2*

Date		*2-17-59*	*2-18-59*	*2-19-59*	*2-20-59*	*2-21-59*
K^+	mEq./L.	6.5	9.1	6.9	5.9	6.4
Na^+		134	127	133	130	141
Cl^-		93	98	93	87	81
CO_2		12	6	9	7	21
BUN	mg. %		100	139	151	
PO_4						16.4
pH		7.11	7.11	7.05	6.96	7.26
			† ↑ ↑ †		↑	

*Two Kayexalate enemas of 30 Gm. each were administered during the evening of Feb. 18, 1959, and a third one in the evening of Feb. 19, 1959.

†ECG. See Fig. 1.

↑ Rectally administered cation exchange resin.

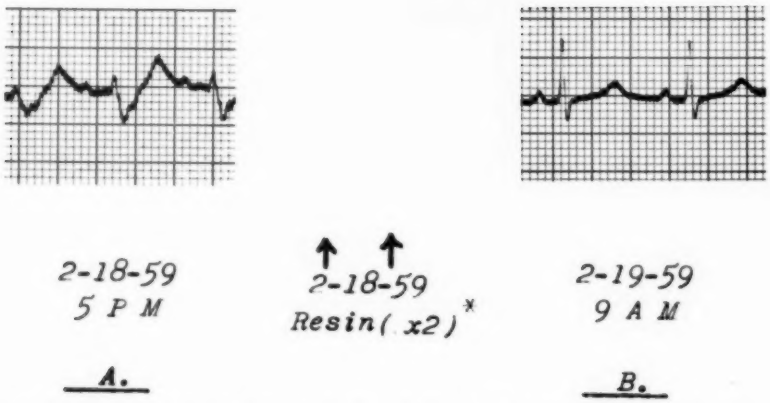

Fig. 1. Lead II electrocardiograms in Case 2, J. H., 2½-year-old Negro male. The two Kayexalate enemas of 30 Gm. each were administered in sequence immediately following the electrocardiogram obtained at 5 P.M. on Feb. 18, 1959. The changes in the ECG pattern are obvious.

*Kayexalate.

were obtained before the first enema and again on the morning of Feb. 19, 1959, at which time the serum potassium concentration had fallen to 6.9 mEq. per liter (Fig. 1). A third Kayexalate enema was given on the evening of February 19, and by the next morning the serum potassium level had fallen to 5.9 mEq. per liter.

In spite of what appeared to be reasonable therapy, the patient remained in the oliguric phase of acute renal failure and died on the seventh hospital day. Autopsy revealed bilateral bronchopneumonia, microcephaly, microgyria, acute renal tubular necrosis, and impacted exchange resin in the colon.

Case 3. R. DiJ. (St. C. H. C. No. 552715), an 8-year-old white male, was admitted to St. Christopher's Hospital for Children on April 9, 1959, with a history of gross hematuria for 2 days. Physical examination on admission revealed no significant abnormalities.

During the first 9 days in the hospital the patient gained 5 pounds in weight (Table III). Distinct but slight oliguria developed. From the eleventh hospital day (April 20) his fluid intake was markedly restricted, and all dietary sources of sodium, potassium, and protein were eliminated.

Enemas containing Kayexalate, 30 Gm. each, were administered on 3 occasions for hyperkalemia and in each instance distinct electrocardiographic changes were observed following the enema (Fig. 2). After 16 additional days of conservative therapy the patient was transferred to Temple University Medical Center for dialysis. During his stay there Kayexalate was administered orally because of melena. He underwent dialysis by means of an artificial kidney apparatus on four occasions. He developed multiple foci of infection and died after approximately 63 days of oliguria. Autopsy revealed severe subacute glomerulonephritis, multiple abscesses (kidney, lungs, and other organs), and the presence of firm, dry resin in the small intestines.

DISCUSSION

Ion exchange resins are high molecular weight polymers with multiple cross-linkages. They are of two general types, anionic or cationic.[8]

The cationic resins are weak acids and are either carboxylic or sulfonic in composition. If hydrogen or ammonium ions are present they are exchanged for "basic" ions (calcium, magnesium, potassium, sodium, etc.). The resin can be presaturated with any cation, depending on the ion to be exchanged. For example, a resin may be charged with sodium for eventual exchange

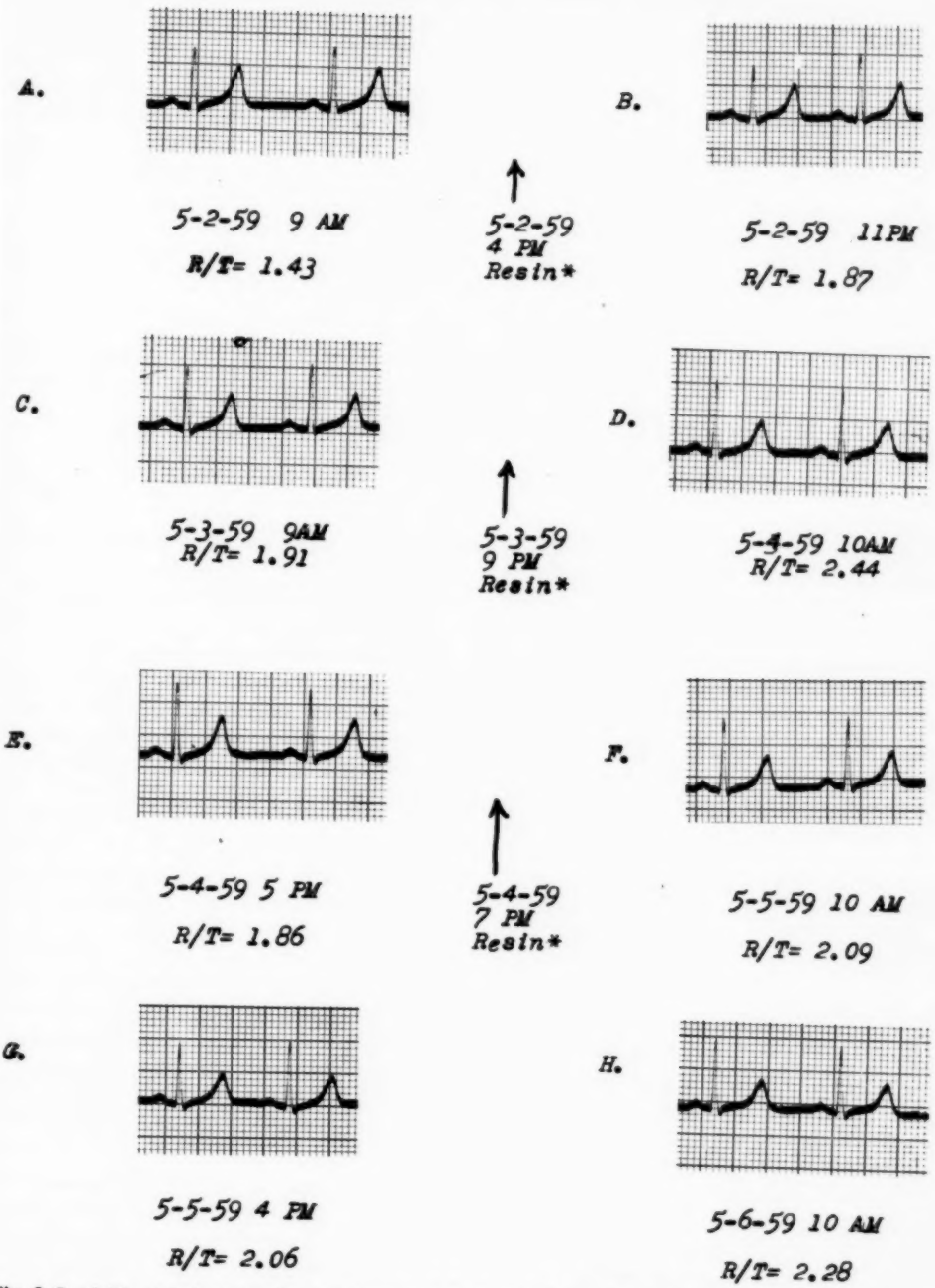

Fig. 2. Lead II serial electrocardiograms from Case 3, R. DiJ., 8-year-old white male. Thirty grams of resin by enema was administered between tracings *A* and *B*, *C* and *D*, and *E* and *F*. Changes in the amplitude of the T waves are subtle in some tracings but are best appreciated by comparison with the amplitude of the corresponding R waves. The ratio of the amplitude of the R wave to its corresponding T wave *(R/T)* is recorded for each tracing. The *R/T* ratio of an electrocardiogram one day after tracing *H* was 2.48. The "peaked" shape of the T wave, especially in tracing *A*, is characteristic of hyperkalemia. *Kayexalate.

Table III. Laboratory data from Case 3*

Date	9	13	14	15	16	17	18	19	April 20
K^+				6.4	5.2		5.3		5.6
Na^+				129	125		123		119
CO_2	mEq./L.			20			19		21
Cl^-				84	82		81		75
BUN	mg. %	54	102	119	110		108		101
PO_4				8.4					
Weight (pounds)		84½	84½	84		87	88½	89	89¼	88¾
Intake (c.c.)		2330	1600	760	2765	1580	1150	1500	1880	2000
Output										
Urine (c.c.)		605+	?(2×)	100	570	730	960	270	270	2600
Vomitus (c.c.)		0	200	135	400	150+	60	290	580	0

*Note the prompt fall in serum potassium values following the first two cation exchange resin enemas. The reason or reasons for the initial drop of the serum potassium level are not known, but in part may have been the result of expansion of the extracellular space by water.

Short arrow, Kayexalate enemas, 30 Gm. each.

Long arrow, Dialysis.

with potassium or charged with ammonium for exchange with sodium. Knowledge of the nature of the charged cation is important, especially in the presence of hepatic failure when the introduction of ammonium ions may be lethal. The high level of ammonia in the intestines of a patient in uremia may diminish the exchange of potassium if the resin is charged with ammonium.[2]

In vitro binding depends upon the concentration of the ion in solution, its valence, and its molecular weight. Binding preference is given to ions of higher valence and higher molecular weight (order, Ca^{++}, Mg^{++}, K^+, Na^+, etc.).

Although soil chemists made the earliest contributions in the field of exchange resins, Dock[9] seems to have been the first to recognize their theoretical implications in medicine. Almost all the data that appeared shortly thereafter were concerned with the removal of body sodium, while very little has been written about the use of exchange resins for the removal of potassium.[10]

In vitro experiments indicate a maximum of 3 mEq. of potassium exchanged per gram of resin. From in vivo experience, however, one cannot expect an exchange rate greater than approximately 1 mEq. of potassium per gram of resin.[2] There is some evidence that the site of greatest potassium exchange in the gastrointestinal tract is the colon.[2, 11]

Kayexalate is an exchange resin in the sulfonated form precharged with sodium. There is no accepted standard dose of this sulfonated resin but some investigators have obtained beneficial results in adults by using from 30 to 60 Gm. of the resin in "solution" administered by high retention enema.[2, 4-7] In smaller children and infants it would seem reasonable to employ correspondingly smaller doses by relying on the exchange rate of 1 mEq. of potassium per gram of resin as the basis for calculation. This amount of resin may be "dissolved" in a small amount (20 to 100 c.c.) of 10 per cent glucose in water. It is recommended that the enema be retained for 6 hours to obtain near maximal exchange of potassium, although a considerable amount of potassium may be removed before this time. The oral route of administration is difficult because of the bulk required and the unpleasant taste; in addition the danger of impaction is greater. These factors have caused oral resin therapy for the purpose of sodium depletion to lose favor.

Prolonged use of any cation exchange material imposes the potential danger of producing hypocalcemia[12]; however, the sulfonated forms seem to possess less affinity for calcium ions than the carboxylic type.[13]

											May					
21	22	23	24	25	26	27	28	29	30	1	2	3	4	5	6
5.3	5.3	5.6		5.2		5.3	5.1	5.6	5.7	5.7	6.9		5.4	5.1	4.7
119	124	124	128	125		124	129	127	126	128	128		130	132	135
21	18	19		17		17		16	12	13	13		13	15	15
75	82	85	82	85		80	85	84	84		88		82	81	84
	95		90	135		81		128	147		173		177		
	13.2						11.9		12.3						
88¾	85¼	86	85	85	85¼	84¾	85	86¼	85½	84¾	85¾		83	82	80½
200	545	450	570	480	815	365	450	385	245	290	425	345	530	425	
450	335	230	90	70	60	15	0	15	8	34	0	20	5	5	
0	0	0	0	0	60	0	0	0	30	0	0	60	0	0	
											↑		↑	↑	↑

It seems unlikely, however, that significant depletion of calcium would occur from the use of resins over relatively short periods of time.

Occasionally the amount of potassium which is removed may exceed expectations and hypokalemia may result (see Case 1). This event may assume added importance if digitalis is being used since potassium is an antagonist to the pharmacologic effects of digitalis.

Fecal impaction is a serious problem and might have assumed even greater proportions in Cases 2 and 3, if these children had survived for longer periods of time.[14] An ingenious method to obviate this problem has been suggested by Pickering and Fisher.[15] They suggest inserting a moistened length of dialysis tubing, which has been sealed at the entering end, into the colon and instilling the resin suspension within the lumen of this tubing. The other end which remains outside of the body is closed and taped to the buttocks. Theoretically the dialysis tubing should offer no obstruction to the exchange of potassium. At the end of the retention period the tubing is emptied of its contents and the entire tubing removed, thus obviating the possibility of fecal impaction. The diameter of the dialysis tubing must be small enough to enable it to be passed a considerable distance into the colon without difficulty and yet large enough to hold a sufficient volume of resin suspension. This limitation might be overcome by maintaining a stock supply of dialysis tubing of various diameters to "fit" infants and children. Another obvious advantage of this method resides in the ability to withdraw samples at timed intervals for potassium determinations. If these samples represent true aliquots, one may arrive at more exact time-dose relationships.

The ability of the resin to control hyperkalemia is suggested by the decrease in amplitude of the T waves in the electrocardiograms and by the decreasing serum potassium levels in the 3 cases herein presented. Although lacking in our 3 cases, there is direct evidence of the ability of the resin to remove potassium and one need not ascribe the drop in serum potassium levels to fluid and electrolyte shifts within the body.[2] The importance of the information provided by these 3 cases is not lessened by their fatal outcome.

Inherent technical problems may render the use of the artificial kidney extremely difficult in infants and young children. When hyperkalemia is the major problem in a patient with renal failure, rectally administered exchange resins may decrease the frequency of the need for vivodialysis or perhaps even occasionally obviate the need

for it. The potentialities of cation exchange resin therapy for hyperkalemia are sufficient to warrant further clinical investigation of its effectiveness and constitute the motivation for this presentation.

SUMMARY

Three cases of renal failure with associated hyperkalemia are presented. In each case the rectal administration of a sulfonated cation exchange resin (Kayexalate) was followed by a decrease in the serum potassium level and in the amplitude of the T waves in the electrocardiograms which were obtained. The clinical use of this resin is described and attention is directed to the potential dangers of such therapy. The literature on the use of ion exchange resins for hyperkalemia is briefly reviewed.

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The response of infants to poliomyelitis immunization after neonatal immunization with triple antigen

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IN A previous communication[1] we reported the first results of a study which had been designed to overcome the risk of "provoked paralysis," an immunization hazard to which attention had been drawn by the Medical Research Council.[2]

This study consisted in immunizing a group of antenatal patients and giving the infants triple antigens—diphtheria, pertussis, and tetanus (DPT)—at 1, 5, and 9 weeks of age under the protective cover of high levels of maternally transmitted poliomyelitis neutralizing antibodies. The present communication gives further details of the responses obtained and includes the subsequent response of the infants to their poliomyelitis immunizations at 9, 10, and 13 months of age.

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PROCEDURES

Immunization of mothers during pregnancy. The expectant mothers were given 3 doses of poliomyelitis vaccine, each of 1 ml. The first dose was given at the time of their first visit to the antenatal clinic (usually about the thirteenth week of pregnancy) when a blood sample was also taken. The second dose was given 4 weeks later, and the third within 6 to 8 weeks of delivery, at which time a second serum sample was taken. At birth both maternal and cord blood samples were collected.

Immunization of infants. The infants were immunized with DPT, 3 doses, each of 1 ml., intramuscularly, at 1, 5, and 9 weeks of age. A blood sample was taken 6 weeks after the last dose. Immunization with poliomyelitis vaccine was delayed until the maternal antibody was expected to have fallen to non-inhibitory levels and then 3 doses, each of 1 ml., were accordingly given at 9, 10, and 13 months of age, respectively. Blood samples were taken at the time of giving

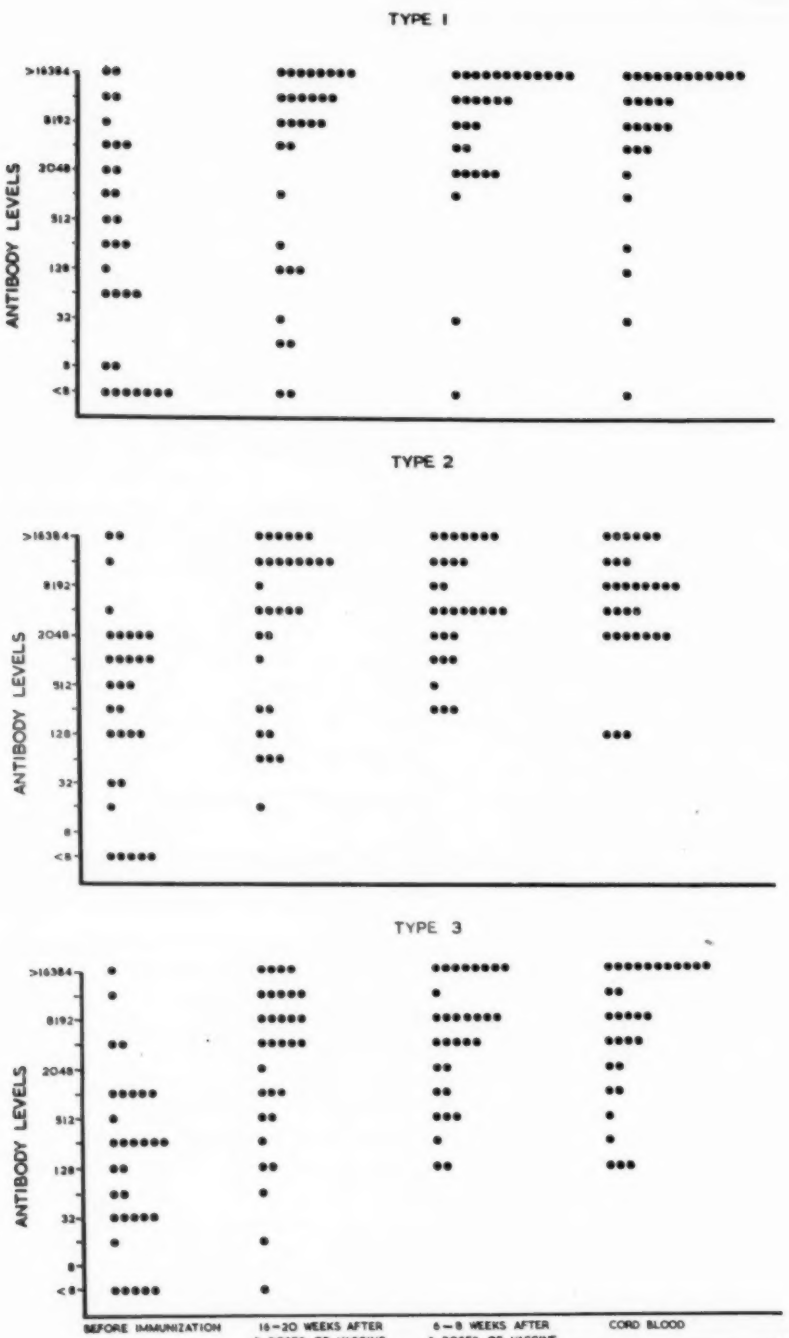

Fig. 1. Antibody responses of mothers given 3 doses of poliomyelitis vaccine during pregnancy.

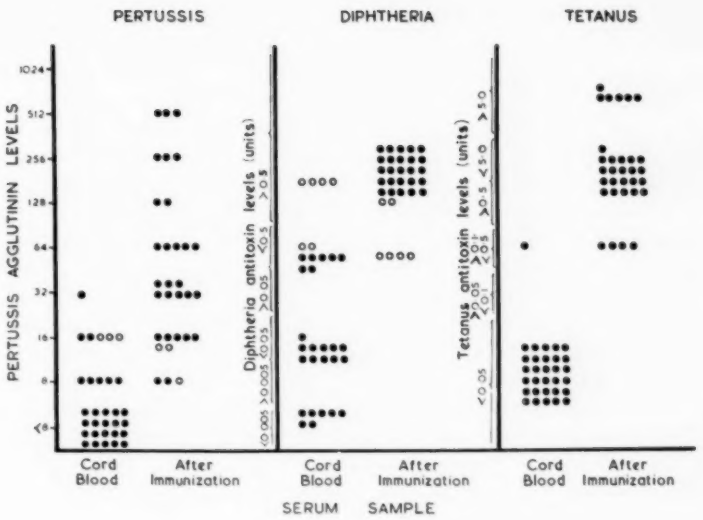

Fig. 2. Antibody responses of infants to 3 doses of diphtheria-pertussis-tetanus vaccine given during the neonatal period.

○—infants giving no responses.

●—infants responding.

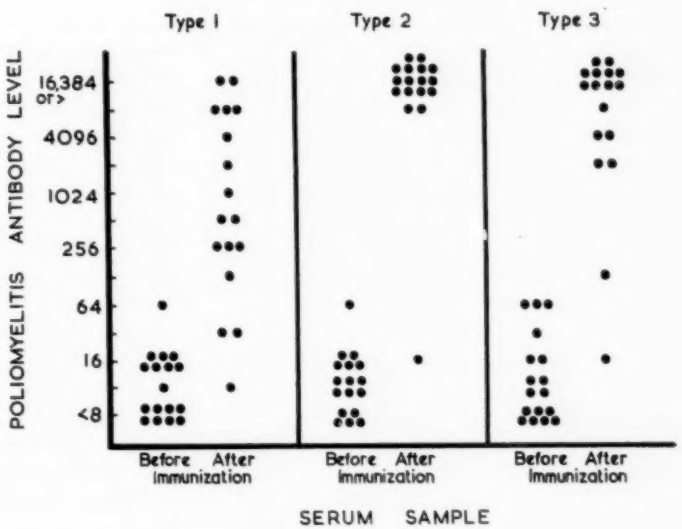

Fig. 3. Primary responses of infants to 3 doses of poliomyelitis vaccine given at 9, 10, and 13 months of age.

the first dose and 10 to 14 days after the last dose.

Vaccines. A single batch of commercial DPT was used, which contained 25 Lf. per milliliter diphtheria toxoid, 20×10^9 organisms per milliliter pertussis, 5 Lf. per milliliter tetanus toxoid, and 2.5 mg. per milliliter aluminum phosphate. The poliomyelitis vaccine* used was prepared from Brunenders (Type I), MEF-1 (Type II), and Saukett (Type III) virus strains.

Titration of sera. Poliomyelitis antibody levels to each of the three virus types were determined by the method previously de-

*Pfizer, Ltd., Sandwich, England.

scribed.[3, 4] For each infant and mother all serum samples were titrated in parallel in the same test in order that a valid comparison of antibody levels could be made. All titers are given as the dilution of serum in the serum-virus mixtures before the addition to cell cultures.

Levels of diphtheria, pertussis, and tetanus antibodies were titrated by the usual methods determining (a) excess diphtheria toxin by intradermal inoculation of guinea pigs after neutralization of toxin-serum mixtures, (b) pertussis agglutinins, and (c) excess tetanus toxin by subcutaneous inoculation of mice after neutralization of toxin serum mixtures.

RESPONSE OF MOTHERS TO POLIOMYELITIS IMMUNIZATION DURING PREGNANCY

The mothers' antibody levels to each of the three virus types during their course of immunization and at their delivery and also the levels in the cord blood are illustrated in Fig. 1.

Before immunization the majority of mothers had antibody to all three types of virus. Of those with undetectable antibody levels (< 8)—7 to Type I, 5 to Type II, and 5 to Type III—only one was triple negative. High levels of antibody persisted for at least 16 to 20 weeks after 2 doses of vaccine in the majority of mothers; only 2 had undetectable levels to Type I, one had antibodies to Type II, and only one had an undetectable level to Type III. After the third dose, however, only one persistently failed to respond to Type I, and all mothers had high levels to virus Types II and III. The antibody levels in the maternal and cord serum samples were strikingly similar.

RESPONSE OF INFANTS TO DIPHTHERIA, PERTUSSIS, AND TETANUS IMMUNIZATIONS

The infants' response to the diphtheria, pertussis, and tetanus components of the aluminum phosphate DPT immunizations is shown in Fig. 2. All the infants with a rise in antibody levels are shown in black circles; those with no rise are shown as open circles. The majority of infants were born with low or undetectable levels of maternal antibody to pertussis and tetanus, whereas there were a number of infants with a detectable level of maternally transmitted diphtheria antitoxin. All but 3 infants responded to the pertussis component, and these 3 were born with detectable agglutinin titers (1:16). Similarly, all but 6 infants gave good responses to the diphtheria component and these 6 were born with high levels of diphtheria antitoxin levels. All the infants except one were born with tetanus antitoxin levels of 0.02 units and all gave an excellent response to the tetanus component.

THE RESPONSE OF INFANTS TO POLIOMYELITIS VACCINE GIVEN AT 9, 10, AND 13 MONTHS OF AGE

Of the 31 infants given DPT, 17 remained in the study and their response to poliomyelitis vaccine is shown in Fig. 3. Although these infants were born with high levels of maternal antibody (Fig. 1), by 9 months of age these levels had fallen to a titer of 16 or less in all but one infant to Type I, one to Type II, and 3 to Type III, and even these had a titer as low as 64. All infants gave an antibody response to three doses of vaccine, the majority having titers of 512 or more to all three virus types. The response to Type II was the best, all but one infant having a titer of 8,192 or more; to Type III the response was almost as good, and, although the response to Type I was not quite so high, it was better than the primary response observed in any group previously studied. The one infant failing to give a good response to Type II also gave the lowest response to the Type I and III components. It is interesting to note that the mother of this infant was one of the lowest responders to the three doses of poliomyelitis vaccine given during pregnancy.

DISCUSSION

Excellent antibody responses were obtained in almost all infants when an immunization

schedule was used in which DPT was given under the protective cover of high maternally transmitted poliomyelitis antibody levels, followed by poliomyelitis immunization when the maternal antibody had fallen to noninhibitory levels. Very high levels of maternal poliomyelitis antibodies were obtained in infants of mothers given three doses of vaccine during pregnancy; the response of those subjects with pre-existing antibody was much greater than those in whom the antibody levels were undetectable. The majority of the infants produced satisfactory responses to the three doses of DPT, but it is interesting to note that the only 3 infants failing to respond to the pertussis component and the 6 infants not showing a rise in diphtheria antitoxin levels were born with the highest levels of maternally transmitted antibodies to these antigens. All infants responded well to the tetanus component.

At 9 months of age the maternally transmitted poliomyelitis antibody levels were no longer inhibitory and of the 17 infants given poliomyelitis vaccine, 8 had undetectable levels to Type I, 5 to Type II, and 7 to Type III. It is not known how long these infants had undetectable antibody levels, which would vary for each individual, but it is clearly an unsatisfactory situation to leave these infants unprotected against infection for indeterminate periods of time. The response to three doses of poliomyelitis vaccine given at 9, 10, and 13 months was exceptionally high to Types II and III and that to Type I was greater than achieved in any group studied so far. How much this can be attributed to the vaccines and how much to the different time schedule (in which the interval between the second and third doses was increased to 3 months) is not clear. The antigenic activity in monkeys of the vaccine used in 9-month-old infants in the previous study[5] was not as high as that of the vaccine used in this study, but both were acceptable. The responses in infants, however, showed a marked difference; in the earlier study, only 1 of 14 gave a Type II response as high as 16,384 whereas in this study 14 of the 17 infants gave such a response. A similar increase was shown with Type III; and with Type I 10 of the 17 infants in this study gave a response greater than the highest level (512) obtained earlier.

Although this immunization schedule has produced satisfactory results, there are two somewhat disturbing features. First, immunization of the mothers with poliomyelitis vaccine gives a wide variation in antibody response, and the infants born of mothers giving the lowest responses will be left for some time with undetectable levels of circulating antibody before poliomyelitis immunization is begun. Second, this schedule involves giving the infants 6 injections which are not completed until the thirteenth month. To obviate these drawbacks we are continuing our studies in an attempt to break through the inhibition by maternal antibodies in the newborn. There are already indications that giving 3 injections of quadruple antigen containing a more potent poliomyelitis vaccine will prove successful. This study will form the subject of a separate report.

CONCLUSION

Active poliomyelitis immunization of a group of 31 infants at 9, 10, and 13 months of age after triple antigen had been administered at 1, 5, and 9 weeks of age under protective passive immunity to poliomyelitis conferred by antenatal immunization of the mothers produced satisfactory results.

Such a schedule has certain drawbacks which make it unsuitable for general use, and the development of an alternative schedule is proposed for the future.

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Changing concepts concerning mastocytosis

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MASTOCYTOSIS has slowly evolved as a new member of the broad group of idiopathic proliferative disorders of the reticuloendothelial system which are loosely referred to as the "reticuloses." Although various European authors have expressed this concept for a quarter of a century, authorities in the Western Hemisphere have generally ignored it. For many decades the sole mast cell disease in man was considered to be urticaria pigmentosa, a chronic, benign, and usually self-limiting lesion confined to the skin. During the past 20 years there has appeared, through numerous isolated reports, evidence that disseminated proliferative disorders of mast cells occur in many clinical forms and may involve not only the skin and regional lymph nodes, but the entire reticuloendothelial system, viscera, muscles, and skeleton as well. Although the concept of systemic mastocytosis is by no means new, it has met with little acceptance by clinicians and pathologists alike. The purpose of this paper is to emphasize mastocytosis as a clearly defined reticulosis and to place it in a nosologic relationship with the so-called "reactive" histiocytoses of unknown etiology.

For almost 50 years following its original description by Nettleship in 1869, urticaria pigmentosa was assumed to be a purely dermatologic condition. In this respect it usually consists of scattered maculopapular, bullous, or nodular lesions (xanthelasmoidea) which tend to urticate when rubbed and which appear histologically as mast-cell infiltrations of the corium with increased pigmentation of the overlying basal epithelial cells. Although the textbooks generally state that it is a rare disease, some 600 cases have appeared in the medical literature.[1] Seventy per cent of the cases are encountered in children,[2] and in 300 cases which were reviewed, 46.1 per cent were discovered during the first year of life.[3] It is not considered to be a familial or hereditary disease, although rare cases of more than one affected member of a given family have been studied, and congenital urticaria pigmentosa in twins has been reported.[3] Recently, isolated mast cell lesions of the vulva were encountered in 2 siblings; however, a search through 5 generations of the family showed no other members to be affected.[4]

In 1933 Touraine and associates[5] suggested that there was more to the entity than a simple cutaneous lesion and proposed that it might also present as a form of "pseudoleukemia." Sézary,[6] in 1936, was the first to use the term "mastocytosis," implying that it was a variety of reticuloendotheliosis. The first histologic evidence of the generalized systemic nature of masto-

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cytosis was published in 1949 by Ellis,[7] who reported the necropsy findings in a 1-year-old female who had been born with urticaria pigmentosa and who died with widespread mast cell proliferation of the skin, connective tissues, lymph nodes, and viscera. Following this isolated observation, other autopsy reports have been published,[8-11] as well as many descriptions of surgical specimens,[2, 12-14] all of which indicated involvement of various tissues and organs by disseminated mast cell proliferations or infiltrations.

The first solitary mast cell tumors were encountered in dogs, and reported in 1942 by Bloom,[15] who proposed the term "mastocytoma" to designate the isolated lesions. Twenty-three cases of solitary lesions in humans followed in the literature, practically all within the past decade. The subject of mastocytomas in man has been amply reviewed by Marshall,[16] who affirms that they are benign lesions occurring in infants, that they are most frequently encountered on the extremities, especially about the wrist, and that they occasionally produce generalized flushing upon manipulation. He is of the opinion that this form of mastocytosis is much more common than we realize, since it is usually mistaken for an ordinary nevus.

REPORT OF CASES

Case 1. A 6-month-old white male was seen by a pediatrician because of a slightly raised yellowish-brown lesion on the lateral aspect of the plantar surface of the left foot. This was a circular area, 1.3 cm. in diameter with slightly irregular borders which had been present since birth.

The obstetric, family, and personal histories were noncontributory.

Physical examination disclosed no other abnormalities. There was no recording of urticarial phenomena, dermographism, flushing, or pruritus. The lesion was removed as an outpatient procedure and submitted for histologic study with no clinical diagnosis.

Microscopic examination of routine hematoxylin-eosin–stained tissue sections showed mild to moderate acanthosis with considerable elongation and slight clubbing of the rete pegs. Within the dermis there was a dense infiltration of plump, round, and polyhedral mononuclear cells which were in in-

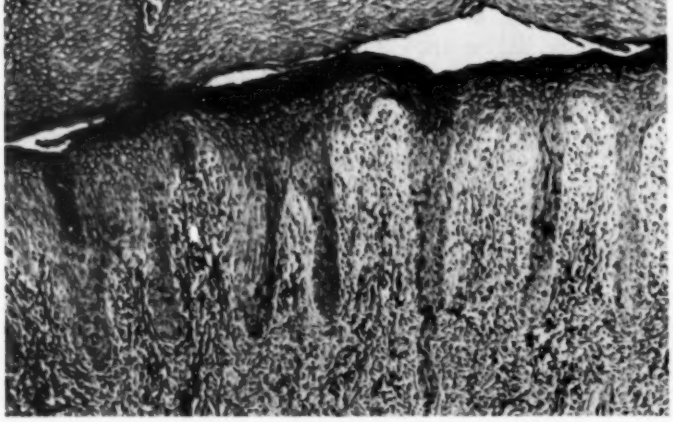


Fig. 1. Photomicrograph of the epidermis and upper corium. There is artifactual separation of the thick stratum corneum. The small dots in the dermis represent nuclei of myriads of mast cells, the cytoplasmic borders of which are indistinguishable at this power of magnification. (Hematoxylin and eosin. Original magnification ×150.)

timate contact with the basal cells of the epidermis (Fig. 1). The major portion of the infiltrate was confined to the upper half of the dermis, expanding many dermal papillae; however, sparse groups of cells extended deep into the corium, accompanying blood vessels and surrounding sweat glands. Under high magnification, minute, indistinct eosinophilic granules were present in the cytoplasm of the cells, and at the periphery of the lesion there was a fine, almost imperceptible granularity of the intercellular ground substance.

The preliminary impression was that the lesion represented some type of histiocytosis; the diagnosis of urticaria pigmentosa was also entertained. A Giemsa stain revealed innumerable small, uniform, red-purple (metachromatic) granules within the majority of the cells of the dermis and spilling out into the intercellular spaces, establishing the diagnosis of mastocytosis.

Case 2. A 22-month-old white male was seen by a physician because of a tan, raised, circular lesion in the antecubital fossa of the right forearm which had been present since birth. No other abnormalities were noted.

The family and personal histories were noncontributory.

Attention was called to the nodule because it was increasing in size, having attained a diameter of 1.2 cm. There had been no complaint of pruritus. In retrospect there had been no notice of urtication, and no attempt was made to elicit the usual clinical manifestations of urticaria pigmentosa since such a diagnosis was not considered. The lesion was removed as an outpatient procedure and submitted for routine histologic examination with the clinical diagnosis of "nevus."

Microscopic examination revealed a dense dermal infiltrate of large, plump mononuclear cells which was considered to be "typical of urticaria pigmentosa." Subsequently, a Giemsa stain demonstrated the presence of abundant metachromatic granules in the cytoplasm of the proliferated cells and established the diagnosis of mastocytosis (Fig. 2).

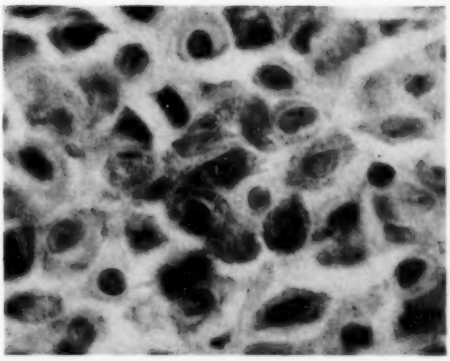
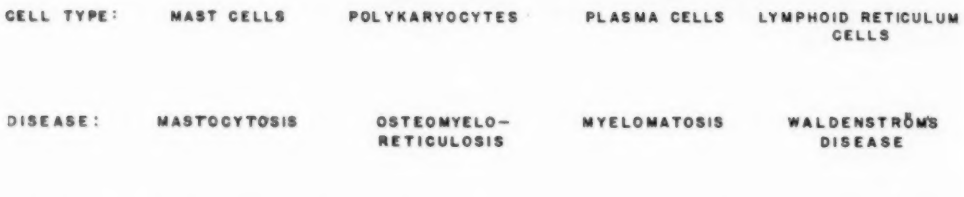


Fig. 2. Dense dermal mast cell infiltrate showing fine cytoplasmic granularity. (Giemsa stain. Original magnification ×1700.)

DISSEMINATED MASTOCYTOSIS

Generalized, acute, malignant, leukemoid, and leukemic forms of mastocytosis are also recognized. Mast cells are rather frequently encountered in the peripheral blood in systemic mastocytosis. A marked increase in hemic mast cells has followed contraction of the spleen after administration of epinephrine.[17] In this case a previous needle aspiration of the spleen had indicated a striking proliferation of tissue basophiles in the parenchyma, and the puncture maneuver itself had caused a rise in the mast cell count of the peripheral blood. Ill-defined leukemoid pictures have been described in cases of the disseminated form of the disease.[9] Reports of true mast cell leukemia are obscured by the fact that many cases of chronic myelogenous leukemia with a blood basophil count of 50 per cent or more have been designated as mast cell leukemia, in some instances by authors who do not make a distinction between the "blood mast cell" and the true tissue mast cell.[18] Nevertheless, the two cells, in humans at least, have been shown to be both morphologically and histochemically distinct (peroxidase reaction),[10, 19] and true mast cell leukemia, though exceedingly rare, has been presented with good substantiation.[10, 20] Thus, based on the accumulated autopsy reports in the literature, and on the extensive clinical observations of such workers as Degos[21] and



INCREASED MALIGNANCY
CELLULAR HYPERPLASIA WITH LYMPHADENOPATHY, HEPATOSPLENOMEGALY
SKELETAL CHANGES WITH FOCAL OR DIFFUSE OSTEOSCLEROSIS. (AFTER ROHR, FROM REMY[23])

Fig. 3.

his associates in France, a definite picture of malignant mastocytosis has been established. It is worthy of note, however, that from a clinical standpoint even the most malignant-appearing case may have a favorable prognosis in regard to life.[16]

As a reinforcement to the histologic and clinical evidence denoting a systemic form of urticaria pigmentosa, rather startling findings were observed by Sagher and associates[22] in 1952, when they discovered bone lesions by x-ray in the ordinary benign form of the disease. A recent review by Poppel and colleagues[1] indicates that of 74 cases which had been studied by x-ray examination 31 presented osseous changes ranging from generalized lesions to localized lytic defects. Stark and associates[13] correlated radiologic findings with histologic studies and proposed the term "mastocytic granuloma" to denote the isolated mast cell proliferations in bone.

As previously indicated, the concept of mastocytosis representing a form of reticuloendotheliosis is not new. A particularly outstanding proponent of this idea in recent years has been Rohr[24] of Zürich, who believes that generalized mastocytosis represents one variety of a related group of several overlapping reticuloses (Fig. 3); closely related lesions are plasma cell myelomatosis, lymphoid reticulum cell proliferation of Waldenström (macroglobulinemia), and "polykaryocytic" proliferation resulting in osteomyeloreticulosis. The idea of the overlapping is based on the observation that cells of one order may be strikingly numerous in proliferative lesions of other cell types, such as the presence of large numbers of mast cells and plasma cells in Waldenström's disease, lymphocytes in myelomas, or plasma cells in myeloproliferative disorders. In this respect, several recent reports have been illuminating. Abundant mast cell proliferation in the marrow has been seen in association with the myeloproliferative syndrome (polycythemia vera),[25] infiltration of the marrow in aplastic anemia,[26] and generalized in association with monocytic leukemia.[11] In order to define these concepts more adequately and as a further introduction to observations which are to be presented shortly, a brief review of several of the cellular elements which

are involved in these processes appears indicated.

MAST CELLS AND HISTIOCYTES

The mast cell was discovered by Paul Ehrlich while still a medical student in 1877,[27] and, in effect, not a great deal has been added to our knowledge of this mysterious element by voluminous investigations of subsequent observers. It was also Ehrlich who first described the basophilic polymorphonuclear leukocyte of the peripheral blood, and who determined that the granules of both these cells were capable of changing the color of certain absorbed dyes. He coined the term "metachromatic" to describe that tinctorial property. He further affirmed that blood basophils were of bone marrow origin, while the "Bindegewebsmastzellen" arose and spent their lives in connective tissue. A number of authorities—Maximow, Ringoen, Downey, Pappenheim, and Michels,[28] to mention a few of the more well known, determined that the mast cells arise from primitive reticulum cells, that they reproduce by mitotic and amitotic division, and that they may be formed heteroplastically by the transformation of lymphocytes, plasma cells, macrophages, or fibroblasts.

It was not until 1937 that Holmgren and Wilander determined that heparin was present in mast cells, and 1953 that Riley and West definitely established that these elements either produced or stored histamine.[27] Although 5-hydroxytryptamine is present in the mast cells of rats and mice, human tissue basophils are devoid of it according to Sjoerdsma and co-workers,[29] Riley,[27] and Cawley and associates.[19]

Mast cells are present in small numbers accompanying blood vessels and are found in all organs and tissues except bone matrix and cartilage. They are increased in number in areas of chronic inflammation or chronic edema, strikingly so in myx-

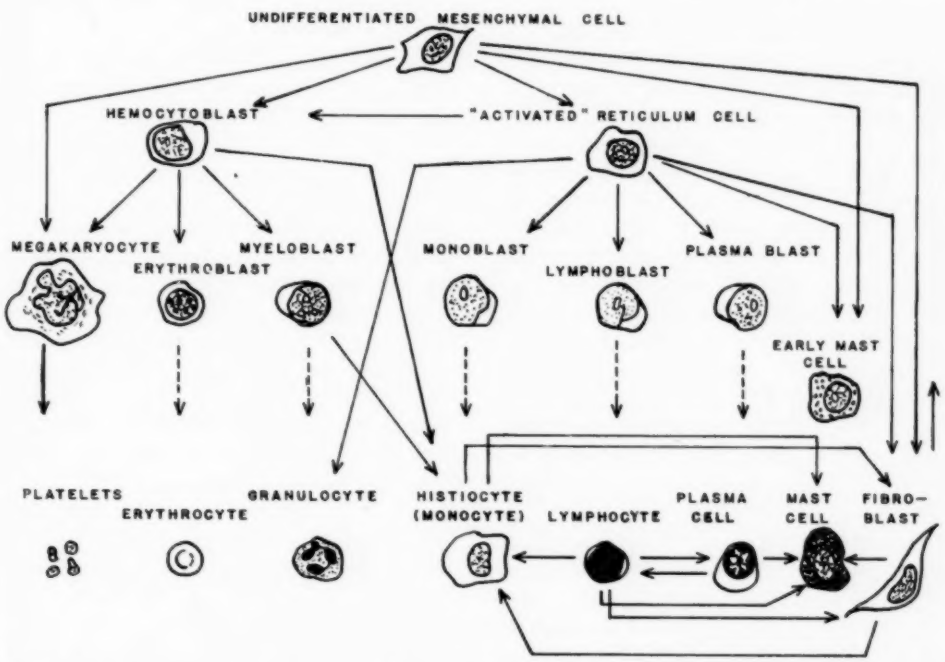


Fig. 4. A schema representing a composite of normal and pathologic lines of development of reticuloendothelial elements as observed in embryos, tissue cultures, and in vivo by various investigators. Other more bizarre pathways have been suggested to explain disease phenomena, but lack adequate demonstration.[28, 35, 36, 39]

edema.[30] They are numerous around gummas, tubercles, and other inflammatory granulomas and are conspicuous in the periphery of certain carcinomas. In the event of a superimposed acute inflammation the existing mast cells promptly disappear from the site of a chronic lesion and, although they are outstanding in young proliferating fibrous tissue, they are quite scanty in old dense collagenous scars.[31] In regard to fibrous tissue formation, an intriguing observation was reported by Morrione[32] and Reilly and colleagues[2] which may explain at least one function of the mast cell. These investigators have shown that the addition of heparin to a solution of collagen produces typical cross-striated collagen fibers which are identifiable by the electron microscope. Reilly believes that the mast cells, in association with fibroblasts, add heparin to the procollagen produced by the latter and thereby play an active role in the laying down of collagen. If this hypothesis is correct, it would perhaps explain the presence of mast cells wherever there is walling-off of chronically inflamed areas, healing of injured tissues, or cicatrization in various types of degenerative processes.

The histiocyte, clasmatocyte, or macrophage is a large mononuclear cell of vascular sinusoidal spaces and connective tissue and is akin to the monocyte of the peripheral blood. On examination of routine hematoxylin-eosin–stained tissues it is not possible to distinguish between the mast cell and the histiocyte in most instances since they both have round or oval nuclei, rare nucleoli, and a light pink cytoplasm. Although there are fine morphologic differences, such as more uniform roundness of the nuclei, and pale, indistinct granules in the cytoplasm of the mast cells, they are usually confused with histiocytes in areas of cellular admixtures unless such stains as Giemsa, methylene blue, or toluidine blue are used to identify the basophilic or metachromatic granules. The mast cell is also frequently fusiform and mistaken for a young fibroblast. Textbooks of dermatology state that dense aggregates of mast cells in hematoxylin-eosin–stained tissues are not difficult to recognize; however, the diagnosis of a mastocytic lesion is frequently and easily missed if special stains and techniques are not applied.[10, 33, 34]

The histiocyte, like the mast cell, may arise from the primitive reticulum cell and similarly may originate from the transformation of fibroblasts and lymphocytes.[35, 36] It has been shown that there is a close developmental and reactive interrelationship among all of the cells of the connective tissue and reticuloendothelial system, and that except for the functional end response, there is a striking similarity between the mast cell and the histiocyte, even to the point that the latter may be converted into the former, and possibly vice versa. A case has been recorded by Asboe-Hansen and Haalund-Jorgensen[37] of an adult with widespread systemic mastocytosis and associated xanthomatosis in which xanthomas and nonlipid "histiocytomas" were interspersed with the usual mastocytic lesions of the skin. The interrelationships of the cells which enter into the formation of the various reticuloses are more easily understood when one views the panorama of the variations in the lines of origin and maturation of the individual elements within the myeloreticuloendothe-

Table I

Histiocytosis	*Mastocytosis*
Solitary lesion	*Solitary lesion*
Eosinophilic granuloma	Mastocytoma
Disseminated lesion	*Disseminated lesion*
A. Subacute or chronic (Hand-Schüller-Christian)	A. Subacute or chronic (Urticaria pigmentosa)
B. Acute or subacute (Letterer-Siwe)	B. Acute or subacute ("Malignant mastocytosis")

lial system (Fig. 4). It is apparent that there is a remarkable side tracking along horizontal pathways, as well as the usual development along vertical lines of maturation, a fact which serves in part to explain the bizarre cellular mixtures in many tumors, leukemias, and granulomas, and the cytologic overlapping in the reticuloses.

MASTOCYTOSIS AND HISTIOCYTOSIS

During the past decade the medical literature has been generously supplied with papers attempting to establish that eosinophilic granuloma of bone, Hand-Schüller-Christian's disease, and Letterer-Siwe's disease are in fact varied manifestations of a single morbid entity to which Lichtenstein[38] applied the term "histiocytosis X." The great majority of authorities are now in agreement with the concept, if not the terminology.

Through the accumulation of data from the many sources which have been mentioned herein, the point has been reached where the entire horizon of mast cell proliferative disorders has come into focus. An examination of the general behavior of mastocytosis discloses a remarkable similarity between it and other reticuloses, particularly the reactive histiocytoses (Table I).

Without attempting to enter into detail on the clinical forms and manifestations of the various disorders outlined above, I have listed a number of features which the two groups, characterized respectively as histiocytosis and mastocytosis, have in common:

1. Each is a "reactive" type of disease in which the proliferative lesions are composed of mature connective tissue elements.

2. Each is nonfamilial, nonhereditary, and not of a primary storage nature, such as Niemann-Pick's or Gaucher's disease.

3. The majority of cases in each group occur in infants and children.

4. There is a tendency toward amelioration or spontaneous regression with increased age.

5. Bone lesions are usually or frequently present.

6. Skin lesions are usually present.

7. Solitary lesions are usually curable by local treatment.

8. Disseminated lesions are not affected by known treatment; however, spontaneous cure is not unusual.

9. There is a generalized specific cellular proliferation throughout skin, muscles, lymph nodes, viscera, and bones in the acute or malignant forms.

10. Specific mature cells may be present in the peripheral blood in the disseminated forms.

11. A corresponding leukemic disease is recognized in each group in which immature forms of the specific cells are present in the blood and tissues (monocytic leukemia versus mast cell leukemia).

There are, however, several features which are at variance in the two groups:

1. There is generally a much poorer prognosis in histiocytosis than in mastocytosis. Although a solitary eosinophilic granuloma may evolve into a fatal disease, the mastocytoma in man has not been observed to do so.

2. Histiocytosis has a decidedly poorer prognosis in the very young, whereas age is not a prognostic factor in mastocytosis. As yet, a sufficient number of cases of fatal mastocytosis has not been studied to be of any statistical significance in this regard.

3. The solitary eosinophilic granuloma is usually, though not always, present in bone, whereas the solitary mastocytoma is usually, though not always, present in the skin.

It might be argued that one obvious difference, based on the functional capacities of the mast cell, widely separates the two diseases from the onset. The object here, however, is not to discuss the clinical differentiation of the entities but rather to attempt to collocate them within their nosologic relationships. Nevertheless, it should be remembered that the functional disturbances in the various forms of mastocytosis are far from uniform, and they have been confused, both clinically and histologically, with Letterer-Siwe's syndrome, leukemias, lympho-

mas, xanthomatoses, and nonpigmented melanocarcinomas when they are improperly studied.[34]

SUMMARY

The majority of papers dealing with urticaria pigmentosa in the past few years have emphasized the concept that the skin lesion is but one manifestation of a systemic reticulosis to which the term "mastocytosis" has been aptly applied. Accumulations of autopsy reports, biopsies, surgical specimens, and some 600 clinical observations in the medical literature indicate that mastocytosis is a disorder which may present itself as a solitary mastocytoma, a benign disseminated disease, or an acute or subacute, malignant-appearing, leukemia-like state. Two illustrative cases of the typical localized form are reported.

There is an intimate interrelationship among all of the cellular elements of the connective tissue and reticuloendothelial system, and a marked histiogenic and morphologic similarity between the mast cell and the histiocyte. An attempt is made to show the expected similarities which, therefore, exist between mastocytosis and "histiocytosis X," both morphologically, and to some extent, clinically.

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Psychophysiologic reactions in the neonate

I. The value of observation of the neonate

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THE immediate neonatal period permits an opportunity to evaluate the human organism in the midst of its first major adjustment—that of survival—utilizing its own resources. The physical reorganization is never again as dramatic or complete, except with catastrophic illness or death. This period of adjustment has been the focus of recent pediatric study with the hope that the physiologic homeostatic mechanisms utilized by each infant would reflect not only the capacity of the infant to respond to the physical stresses of extrauterine survival, but might also help in understanding the extent of stress undergone in the birth process and its effect on the particular infant. Dr. Clement Smith[6] summarizes many of the physiologic normals in his book on the *Physiology of the Newborn,* and suggests variations within normal limits which may have significance in retrospect and in future prediction of the use of the infant's physiologic equipment. We are attempting to study similar aspects of psychophysiologic homeostatic mechanisms, relating their style of adaptation to these same stresses to the future psychological capacities of the individual.

Phyllis Greenacre[3] in her excellent book, *Biological Economy of Birth,* expresses the tenet that each infant reacts in a characteristic way to the birth process and to the anxiety prototype it creates, and she predicts that it may influence his future emotional adjustment. Study of the neonate's psychophysiologic adaptive mechanisms in the first week after birth might reflect his individual ways of adapting to the birth process, and give us some understanding of their immediate use in extrauterine life, as well as their future value in adjusting to his particular environment. Since the demands of physical reorganization are so great in the first week, any single set of observations aimed at individual constancies of psychological importance may be masked by more dramatic physiologic changes. But a repeated, day-to-day evaluation under comparable circumstances might neutralize some of these effects and reflect more adequately the infant's psychophysiologic adaptive potentialities. Observation is a clinical tool used daily by pediatricians on which reliance is placed, but its scientific value is often questioned.

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From the standpoint of a pediatrician, a simultaneous evaluation of the individual properties of (1) the purely physical systems and (2) the psychophysiologic adaptive mechanisms with their capacity to be influenced by environmental stimuli would be ideal. To be able to predict for oneself and, to a judicious extent, for the mother the particular characteristics of her infant would multiply one's value many times in supporting the evolution of the best possible mother-child relationship.[1] As pediatricians we must be impressed by the strength of the neonate to survive the exigencies of the birth process and the major adjustment to extrauterine existence. His innate strength is also evidenced in supporting his own individuality and in influencing the environment to adjust to him in a particular way, consistent with his characteristically individual needs.

THE INFLUENCE OF A DIFFICULT NEONATE ON THE MOTHER-CHILD RELATIONSHIP

The following example is that of an infant who presented particular difficulties at birth to a young mother, and with these he influenced her particular capacity to mother him to a marked extent. These difficulties were apparent in repeated observations made in the neonatal period. It is obvious that the outcome was not entirely dependent on his constitutional equipment at birth, but his difficulties quickly became reinforced by the interaction between him and his environment. It is also evident that this particular baby exerted a strong influence in determining the outcome of the mother-child relationship.

George was the first child of professional parents. The father was a 30-year-old nonmedical research professor at a local medical school; the 28-year-old mother also was a scientist. The baby arrived after 5 years of marriage and of saving "to have a baby." The mother expressed delight in her pregnancy when she came to see me and voiced her determination to breast-feed her infant because it was a family tradition, and she wanted to be like all the other women in her family. She arranged for no medication to be given during labor and received none despite a 12 hour labor. Her husband was at her side throughout labor, recording in detail every pain, its duration, type, etc. After 12 hours of labor she was transferred to the delivery room where spinal anesthesia was administered, the baby's head which was "stuck on a rim of cervix" was dislodged, and delivery followed immediately. The infant cried at once, his color was excellent, and he showed no signs of distress. The birth weight was 8½ pounds, the head was molded, and the baby had a big frame. Findings on physical examination on the day of birth were normal.

On observation the baby characteristically exhibited two states and they were constant throughout his hospital stay. They were extreme states and the transition from one to the other was strikingly rapid, even though he showed a marked resistance to changing from one state to the other. Observations were made for varying periods of 30 to 60 minutes in the nursery, in a quiet, single room without disturbing stimuli, and with the mother.

The first state. A deep sleep appeared to be the first state in which he was quite floppy, with poor muscle tone, and with little spontaneous movement or any startle reaction present. The baby was difficult to rouse; stimuli caused little reaction other than brief respiratory changes, mild startles, or blinks, but no change in alertness. When picked up and held in this state, he adjusted briefly with some muscle tone, eyes opened briefly, then he resumed his limp original state. Talking to him, stroking him, even undressing him had little but a transient effect on him, and one was struck by his refractoriness and his capacity to maintain this flaccid, relatively unresponsive state.

The second state. This consisted of screaming, hyperactivity, and hypersensitivity to stimuli. His activity consisted of constant thrusting, thrashing movements of the extremities intermingled with cyclic reflex startling to his own sudden movements. In this state, he seemed overreactive, and

any mild stimulus seemed to perpetuate this activity. A major stimulus, such as a loud noise, bright light, or air blast to the abdomen was able to break through and briefly quiet him, following which his activity quickly reached a peak. This hyperactive state maintained itself for long periods, 15 to 20 minute periods being observed. The continuous hyperactivity interfered with any organized behavior, such as hand-to-mouth, visual fixation and following, sucking on a nipple, or any spontaneous quieting. Major restraints, such as swaddling or holding the legs flexed on the abdomen, were necessary for long periods to quiet him, and these restraints were finally instituted to facilitate nursing. As he became quiet, he very rapidly lapsed into the deep sleep state described above, thus effectively shutting out the environment.

Since these two extreme states persisted after the first 5 days when the effects of delivery should have worn off, a neurological consultation was sought, and a lumbar puncture was performed. Examination of the cerebrospinal fluid did not reveal any abnormalities. The neurologist* found no evidence for central nervous system damage and concluded that the infant was neurologically intact; however, he considered that the extremes of state, together with the refractoriness to stimuli and the capacity to maintain these two different states for such long periods, were definitely unusual.

The effect which this unreachable baby had on the new mother, with her determination to nurse, was dramatic. She became depressed over his "rejection of her," wept a great deal, ate poorly, and, as a result, was less and less effective in handling this maverick. With assistance from the nurses and the pediatrician, and by swaddling, after 7 days the baby began to nurse effectively and gained enough at the breast by the eighth day so that he could be discharged. At home, each breast feeding was a stormy 1½ to 2½ hour period, with the mother weeping and the baby screaming—"a nightmare of who would outlast the other." The mother remained determined to nurse in spite of everything. The baby had long periods of screaming each day, totaling 6 to 8 hours, and could not be quieted by any of her maneuvers. The mother kept a detailed diary of each day and minute by minute recorded her unsuccessful, anxious attempts to reach her child. This screaming, thrashing pattern blended imperceptibly with another kind of unreachableness by 4 to 5 months in which he would lie in his crib staring at a bird mobile above him or at his hands for long periods, and he seemed little gratified by being played with or held by his anxious, depressed mother. His father throughout all this could get a better response from him, but said "he is not as much fun as I expected him to be," and withdrew to his laboratory. The mother spent a part of every day in communication with her pediatrician and the baby was seen frequently to reassure her. No neurological or physical abnormality was ever found. The baby gained rapidly and seemed entirely healthy.

At the 5 months' examination the infant lay on the examining table and seemed unreachable, as if he didn't see or hear. However, he had the usual startles and blinks which indicated that his sensory apparatus was intact. After the examiner continued to talk to him in a soothing, quiet voice, he finally responded and began to look at the examiner. After some 20 minutes he even smiled briefly and allowed himself to be held, looking away from the examiner's face. (Earlier, he had screamed constantly until he was put down.) After 30 minutes, he responded to the examiner by adapting his body to the examiner's arms, and with a look and a brief smile. This was upsetting to the mother, however, and she commented bitterly on how unusual this response was. As she took him from the pediatrician, he began to scream pitifully and her eagerness changed to rigid anger.

Motor development was slow all along, but there was always evidence of a capacity

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to perform. The social responses were particularly uneven, and he was observed by a psychologist* on several occasions. The postural development was stationary from 5 months on, little attempt was made to sit, none to creep or crawl in prone position, and he showed active resistance to being stood up. He sucked his fingers very little and, according to the mother's detailed diary, made infrequent sporadic overtures to the objects on the crib or in the play pen. He either cried when in new places or became silent and immobilized.

By 7 months his mother felt driven to seek psychotherapy for herself and continued such treatment for 1½ years. After 2 months of the mother's therapy the infant must have sensed a difference in her feelings about him, for the mother observed, "at last I can see George as he really is. I always thought it was just my fault." The child began to make progress and came along less slowly. He sat alone at 10 months, stood at 14, walked alone at 20, put words together by 28 months. He has made increasing progress socially. At 6 or 7 months of age he could not be taken out of the house without screaming constantly or withdrawing into an immobile mass. However, now at 2 years of age he could be taken to visit other smaller children successfully. By 2½ he played on an equal level with 2-year-old children, and his mother and father had the courage to have another baby.

This second child, a boy also, was an easy, attractive, outgoing infant from the first. The mother nursed him for 9 months and had great delight in him, although she constantly reiterated that "George comes first." George regressed briefly after his mother's return from the hospital and sat immobilized for long periods. Then he seemed to profit from the general happiness and relief in the familly, and he has continued to progress more normally. His mother still says, "He knows how to win any struggle with me. He just screams or acts as if he cannot see or hear me, and I cannot fight back."

*Grace Young, Chief Psychologist at James Jackson Putnam Children's Center, Roxbury, Mass.

DISCUSSION

Throughout the pediatric relationship with George and his mother, one felt that an early prediction of his difficult characteristics and some sort of elaboration of the limitations of his responses to *any* environment might have relieved some of the anxiety and guilt which furthered her incapacity as a mother to him.

The problems involved in any prediction in this case centered around (1) reliable evaluation of the neonate and (2) an understanding of the mother which would enable one to foresee her use of such predictions. Since the goal for such a prediction was to enhance rather than endanger the incipient mother-child relationship, it was of primary importance that one follow her cues, allow her the necessary dependent relationship on a supporting figure, and use one's understanding of the neonate to free her of her own incapacitating feelings of guilt and inadequacy as a mother.

The evaluation of the infant's observed behavior in this first week centered around the differential between innate characteristics and the more transient disorganizing effects of labor, delivery, and of the energy utilized by physiologic homeostatic mechanisms involved in adjusting to an extrauterine existence. That this infant reacted in a particularly disorganized fashion was obvious. Although pediatric and neurological evaluations seemed to rule out gross pathology of the central nervous system, clinical observation suggested a marked deficit in responsiveness in the first week. This was disturbing to the young mother, and it was reassuring to her that the pediatrician felt it was a part of the baby's unresponsiveness rather than her inability to perform proficiently as a new mother. This enabled her to continue her breast-feeding efforts. However, had we had better methods for predicting the innate characteristics in this infant, one wonders whether a more assured prediction of the possible difficulties

for her would have relieved more anxiety in the first few months of adjustment.

The disturbance in the mother-infant relationship was apparent at all times, and the withdrawal mechanisms which the infant utilized very early suggested those used by schizophrenic children. This ominous possibility necessitated intervention of a more drastic kind than pediatric prophylaxis, and the mother's psychiatric help seemed to turn the developmental tide. Whether this infant had a deficit of the kind which was particularly susceptible to a difficult, unrewarding early environment, or whether this withdrawal could have been changed any earlier with any set of environmental stimuli is open to question. This baby stressed our need for the development of more sensitive methods for evaluating the innate capacities and limitations of newborn infants early. In dealing with other less disturbed situations which have comparable elements, this kind of newborn infant points out the value of more understanding of neonatal equipment in all babies.[2, 4, 5] With more reliance on early observation and evaluation, we, as pediatricians, might further the interaction of the neonate with his environment in a positive direction.

SUMMARY

The case of a difficult, unreachable newborn infant is presented, with an estimate of the effect on the mother-child relationship. The value of reliable observation of innate characteristics of the neonate and the value of their predictive use in relieving maternal anxiety are stressed.

I wish to express gratitude to Stewart H. Clifford, M. D., for his advice in the revision of this paper, and to Marian C. Putnam, M.D., and Mrs. Grace Young for their insight and assistance in understanding the case presented.

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Psychophysiologic reactions in the neonate

II. Effect of maternal medication on the neonate and his behavior

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ANY evaluation of individual innate adaptive mechanisms in the first week of life seems dependent on variables which strongly influence the capacity to achieve homeostasis. (1) Prenatal influences, such as hormonal, neural, viral, hematologic, etc.; (2) the relative maturity at birth of the central nervous system and of the total organism; (3) the effects on variably immature organ systems of medication and anesthesia given the mother prior to and during delivery; and (4) the kind and duration of delivery, trauma, and anoxia—all influence the infant's adjustment in his first week. They must be taken into account as variables influencing his adaptive capacity.

One of the most striking effects on the newborn infant's ability to adapt to the environment in the first week of life seems to be the effect of the accumulation of a drug in the infant as a result of predelivery medication given the mother. When the dose is large enough and administered sufficiently prior to delivery, an effective level of medication may be transmitted via the placenta to the infant.

Blood levels in the infant tend to be in direct proportion to those in the mother. The decrease in circulating levels of barbiturate-like substances in both mother and infant seems to be primarily dependent on detoxification of these drugs by the mother's liver.[4] The level in the infant at birth depends upon the time of separation from the mother after the drug is given. Also, there is some evidence in favor of a selective storage of barbiturate in the immature brain and cerebrospinal fluid, so that there is a lag in the decrease in the level of the drug in the fluid bathing the brain.[4] In immature animals, Fouts[2] found that the brain was particularly susceptible to the effects of barbiturates. Not only was there a deeper depressing effect, but it was also more prolonged in the immature brain.

The immature liver possesses a minimum of enzymes necessary for detoxification of these drugs.[3] The newborn infant's liver is overtaxed with "blood-breakdown" products, so that the detoxification of drugs may proceed slowly.[5] These are some of the reasons for inadequate detoxification, and there is

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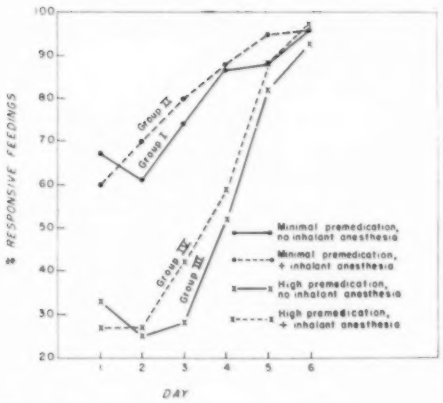

Fig. 1

evidence that there are appreciable circulating levels of barbiturates in the neonate for a week after delivery.[4] The infant seems physiologically designed for both an immediate and a more prolonged effect of depressant drugs on his immature central nervous system.

GENERAL OBSERVED EFFECTS

A comparison of infants whose mothers were given effective doses of sedative and analgesic drugs with those of mothers who had little medication prior to delivery led us to make some generalizations based on clinical observation:

1. All babies seem quite alert and responsive to sensory stimuli for a few hours after delivery, e.g., (a) they fix and follow a red ring visually for several minutes at a time; (b) they hear, attend, often even turn their heads to mild auditory stimuli; (c) they become quiet quickly in response to warmth, to changes in position, or to auditory and many other stimuli.

2. There follows a relative state of disorganization which seems to last for 24 to 48 hours in babies whose mothers were given no medication and for 3 to 4 days in babies of heavily medicated mothers. Disorganizing effects seem to occur as a normal result of birth and recovery processes, but they are accentuated and prolonged by medication. The extent of relative central nervous system disorganization or depression seems positively correlated with the type, amount, and timing of the medication given the mother. Inhalant anesthesia has a more transient effect than premedication, such as a barbiturate.

A typically affected baby may lie quietly for relatively long periods of time in a flexed position, with eyes closed and with slow, deep, regular respirations. Respiratory irregularities from time to time reflect responsiveness to external or internal stimuli, but they are transient and short-lived responses for the most part. Skin color is affected by reduced cardiovascular activity and the extremities are mottled. This state resembles the "regular sleep" of infants described by Wolff,[6] but in this period there are fewer, less generalized startles, and spontaneous activity or responsiveness may be confined to brief respiratory changes or to isolated movements of small body segments, such as facial grimaces, twitching of fingers, toes, and the like. Moderate stimuli such as auditory or visual ones may penetrate this sleep state but with some latency, and the response is diminished. Stronger stimuli or tactile and temperature changes disturb the baby more quickly, and there is a rapid spread of disturbance to all parts of the body. There is a lack of modulation or suppression of cyclic general movement in this state, and reflex activity may perpetuate itself with startles for relatively long periods. The movements themselves are jerkier, are often restricted to certain planes, and have more of the snapback which is characteristic of immature babies. In most babies this depressed state is intermingled with some of the more normal periods of alertness and responsivity to the environment seen in less disorganized states. But there are many intervals of hyperreactivity and hypersensitivity to internal and external stimuli. In these hyperactive periods they are also relatively refractory to change in status. The rapidity of change from one extreme state to another is striking. None of the modulation seen later may be present. Refractoriness to external stimuli and a capacity to maintain these relatively unresponsive states of deep sleep and hyper-

actvity are notable and characteristic of this period.

EFFECT ON BREAST FEEDING

That this transient period has a marked effect on the incipient mother-child relationship seems obvious as one tries to implement the breast feeding situation in the first few days between a young, eager, anxious primipara and her sleepy, difficult-to-alert, unevenly responsive baby. In order to compare the difficulties that might arise in this area alone, 41 multiparas who were breast feeding for the second or third time were asked to register their impressions of the alertness and the readiness of their infants to nurse. Their subjective impressions were evaluated on the basis of (1) how long an interval of stimulation was necessary to alert the baby and (2) how effectively responsive they were during the nursing period. The infants were given credit for a good nursing period if (1) they nursed after 3 consecutive minutes of vigorous attempts at arousal, and (2) they were alert and nursing for 3 minutes per nursing period in the first 2 days and 5 minutes per period thereafter.

The routine at the Boston hospitals,* where this study was done, is to take the babies to breast once at the end of 24 hours, twice in the second day, 3 times in the third day, and 5 times in each of the fourth, fifth, and sixth days. These 41 mothers were multiparas who had nursed babies before; we felt this might eliminate some of the "first-baby apprehension" in our results. The mothers were told this was a study to determine the amount of assistance which was required from the nursing staff to enable a new mother to start her baby nursing. They were asked to record at each feeding their impressions of (1) initial alertness on the part of their babies, (2) the difficulty involved in awakening them i.e., how long it was necessary to stimulate them and how much stimulation was necessary to institute active nursing, and (3) how long during the feeding period this state could be maintained with only the usual stimulation. The day the baby began to regain weight was recorded. No supplementary formula was given these babies. All babies were intact from a physical and neurological standpoint as far as could be determined by repeated examinations. None had had complicated or prolonged deliveries.

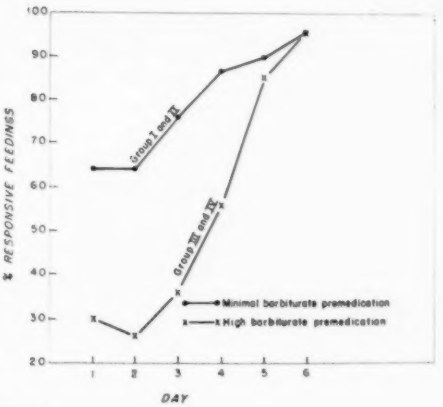

Fig. 2

The babies were placed in one of four groups according to the amount of medication and anesthesia given to their mothers during labor.

I. Anesthesia. Spinal, saddle block, or pudendal block or none.

Premedication. Scopolamine, not more than 0.04 mg. (routine); barbiturates not exceeding 60 mg. during the 1- to 6-hour period prior to delivery; no Thorazine, tranquilizer, or other medication was given in that period.

II. Anesthesia. Inhalants, such as ether, trichloroethylene, Nisentil, or nitrous oxide which effectively anesthetized the mother so that she could not remember the delivery.

Premedication. As above in No. I.

III. Anesthesia. Saddle block, spinal, or none.

Premedication. More than 150 mg. of barbiturates or like substances given as early as 1 hour and not more than 6 hours prior to delivery. Scopolamine as in No. I.

IV. Anesthesia. Ether, gas-oxygen, Nisentil, or other inhalants with which the mother

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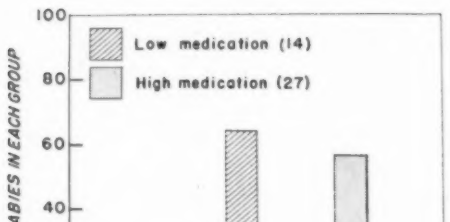

Fig. 3

was anesthetized at the time of delivery as noted on the mother's chart.

Premedication. As in No. III.

These groupings were made on the assumption that premedication to the mothers of Groups I and II would not greatly affect the course of the infant, but that it would affect that of the infants of Groups III and IV, and that the maternal anesthesia would affect the infants of Groups II and IV, but not those of Groups I and III.

An effective feeding situation was considered to be one in which not more than 5 minutes of stimulation was necessary to rouse the baby, and in which he nursed for at least 3 minutes in each period of the first and second days and 5 minutes in each period of the third through the sixth days. The results, as recorded by the mothers, were based on subjective evaluations and perhaps even wishes; in addition, there were many other important variables for which we did not attempt to account, such as (1) duration of labor and its effects on the baby and the mother and (2) how the anesthesia and medication influenced the mothers' handling of the infants during the first few days.

EFFECT OF PREMEDICATION AND ANESTHESIA ON RESPONSIVENESS TO THE NURSING SITUATION

There is such wide divergence between the results obtained in Groups I and II versus III and IV, as demonstrated in Fig. 1, that they are combined in Fig. 2 to show the relationships to medication with barbiturates. Inhalant anesthesia administered to the mother during delivery seemed to be relatively unimportant in relation to alertness for nursing; there was a slight positive effect which is difficult to explain. Whether this positive effect signifies more effort on the part of the mothers to rouse their infants or whether anesthesia acts as some sort of protection against the effects of premedication is not answerable by this study.

EFFECTS OF PREMEDICATION ON THE NURSING SITUATION

The data for the first day are based on a single feeding, and it must be recognized that there may be many variables in addition to the barbiturate premedication given the mother which can influence the results obtained. In this group of babies, the reports show a wide divergence in responsiveness to the feeding situation on the first day. Sixty-five per cent of the feedings in Groups I and II were effective; but in Groups III and IV only 30 per cent were effective. There is an early significant difference between the responsiveness of babies whose mothers were given little or no barbiturate premedication according to these data (reliability of the difference between the two groups is equal to 0.03).

On the second day, the data are based on 2 feedings, hence it has more significance in denoting a difference in responsiveness of the two combined groups of babies. In the group of babies whose mothers had little premedication, feedings were 65 per cent effective. Only 25 per cent of the feedings were successful in the more heavily medicated group. This difference of 65 per cent versus 25 per cent shows a reliable significance of $p = .002$.

On the third day, the two groups varied considerably in their responsiveness to feedings—75 per cent were successful in the group with little medication, in contrast to 35 per cent in the more heavily medicated group. Since there were 3 feedings per day,

the significant difference shows a reliability of $p = .001$.

On the fourth day, the infants in the group with little premedication responded to 87 per cent of the feeding situations, whereas those in the more heavily medicated group showed responsiveness to 55 per cent. Based on 5 feedings in each group, there was a significant difference with a reliability of $p = .001$.

By the fifth and sixth days, the infants in each group were reported to be awake and alert in most of the feeding situations (over 85 per cent), and there was no significant difference in their ability to nurse.

In the two groups of babies, whose mothers received little or no barbiturates, the number of effective feedings increased from 60 per cent on the first 2 days to more than 75 per cent on the third day, and to 87 per cent by the fourth day.

In the groups of babies whose mothers received large doses of barbiturates prior to delivery, there was a 5 day interval before 85 per cent of their daily feedings were successful.

Thus there seems to be a marked difference in the effectiveness of the early postnatal feedings in the two groups, and a difference of 48 hours between the two groups in attaining effective feedings in 75 per cent of the daily trials.

Fig. 3 shows the 24-hour difference between the two groups (p significance beyond the .001 level) in the beginning of effective weight gain of the babies.

Several conjectures may be made for this significant difference in the beginning of weight gain in these babies. These include: (1) a difference in the mother's ability to awaken the baby because of effects of medication on her, (2) less effective stimulation of the breast by the sleepy baby so that milk production is delayed, (3) a delaying effect of medication on the production of milk, and (4) a delay due to medication of the neonate's physiologic ability to utilize breast milk. None of these possibilities have been examined in the literature and are entirely speculative at this point.

DISCUSSION

The evaluation of neonatal differences, normal as well as pathologic, is of great importance to pediatricians. Innate individual differences in newborn infants are estimated consciously and unconsciously by any new mother. Pediatricians observe these differences in their clinical evaluations, but are often unwilling to place values on them. Further studies of neonatal differences should provide more definitive bases for evaluation of the individual infant and more confident scales within which they can be rated. But, in order to understand inborn and more lasting differences between newborn infants, we must also account for the transient effects of many external variables. Around the delivery process, there are many variables which cannot be evaluated at present. The effects on the neonate of drugs administered to the mother may last long enough to produce certain predictable patterns. These observations on the effects of drugs on the recovery process, and specifically on the ability of the infant to adapt to nursing, are a precursor to more detailed observations of psychophysiologic changes in the neonate during the first week of life.

We hope to attain further understanding of the uses of his adaptive capacities. We wonder whether the disorganization caused by these depressant drugs might not accentuate as well as prolong the recovery process and make it more available to scrutiny. Thus, individual differences as well as day-to-day differences in early adaptation might be more easily discernible. The effects of different kinds of deliveries on the neonate might then be estimated. The evaluation of individual differences in adaptive capacity for the prediction of growth and development potential could be of inestimable value to the pediatrician in preparing the mother for her role with her particular infant.

SUMMARY

Certain observable differences in behavioral patterns of the newborn infant as he recovers from the delivery process are

recorded. The influence on these patterns of depressant drugs given the mother as premedication is seen as a deepening and prolongation of the central nervous system disorganization attendant on the birth process. The usual period of general disorganization seems to be prolonged for 1 to 2 days by relatively heavy premedication with barbiturates.

In the neonate's specific ability to adapt to the breast-feeding situation, this study of 41 babies demonstrated a lag of 48 hours' duration. Weight gain in the observed infants was delayed 24 hours by relatively heavy barbiturate premedication given the mother.

The importance of accounting for the effects of drugs on individual responses in adapting to extrauterine existence is emphasized.

I wish to express my gratitude to David Gallant, Psychologist, at the Boston Lying-in Hospital, Boston, Mass., for his assistance in the summarizing of the data.

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The relationship of growth and differentiation in the developing embryo

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CONSIDERABLE work has been done to elucidate the mechanisms controlling tissue and organ differentiation in embryonic development.[1] It has been demonstrated that many stimuli, acting either on the embryo itself[2] or on the external environment,[3] can alter differentiation. Little is known about the effects of such external stimuli on subsequent growth of the embryo and even less on the relationship of tissue and organ differentiation to total growth.

The present experiments were designed to study the effects of starvation and anoxia on total growth and differentiation. The interrelations of tissue development and total growth were also explored by studying the effect of increased differentiation on total length. The larval salamander *(Ambystoma opacum)* was chosen because of its unique ability to regenerate entire limbs by a process quite analogous to embryonic differentiation.[4]

METHODS

Anoxia experiments were carried out by removing feeding stage larvae from water for 5 minute periods once daily for 5 days. Total length was measured with a standard steel millimeter rule, and differentiation observed by counting the development of hind limb digits. Beginning with the two digit hind limb, an additional finger appears approximately every 10 days.

Regeneration experiments were carried out by amputation of both forelimbs in the midradial areas. Control animals had a similar amputation, leaving a skin flap which eventually closed over the wound and prevented regeneration.

RESULTS

Total starvation of larvae for 20 days produced an immediate decrease in weight and volume. Linear growth showed no retardation for approximately 7 days with differentiation proceeding normally throughout the entire period. In Fig. 1 the experimental animal on the right is notably thin and slightly retarded in linear growth, but hind limb differentiation is normal.

Exposure to anoxia produced a more marked retardation of linear growth for a period of 10 to 20 days following the anoxia. In Fig. 2 the animal on the right, 20 days after exposure to anoxia, is considerably smaller than the control. Hind limb differentiation again proceeds at a normal rate.

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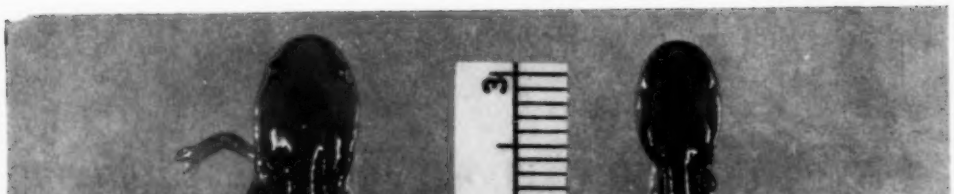

Fig. 1. *Ambystoma opacum* larvae. Left, control. Right, after 20 days of starvation.

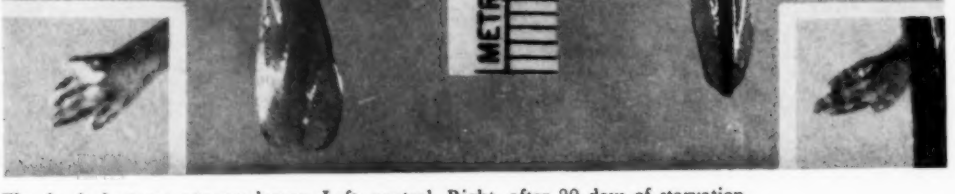

Fig. 2. *Ambystoma opacum* larvae. Left, control. Right, 20 days after exposure to anoxia.

Fig. 3 summarizes the experimental data obtained with anoxia and starvation. Each dot represents one animal. Growth in millimeters for a 20 day period is plotted for control and experimental animals. It is obvious that anoxia exerts a more profound growth-stunting effect than starvation. In both cases, however, differentiation of the hind limb proceeds normally.

Growth then does not seem to be a major stimulus to differentiation. Is differentiation a stimulus to growth?

Limb regeneration in this species affords a unique means of studying the effects of differentiation on total growth. Fig. 4 diagramatically traces the process of limb regeneration following amputation. A blastema forms in the first 10 to 12 days; the cells of this knob of undifferentiated tissue resemble early cells and behave functionally[5] and biochemically[6] like embryonic cells. Over the next 10 to 12 days these cells differentiate into a structurally complicated, completely functional hand. If a skin flap is left at the time of amputation, no regeneration takes place. Such animals, as well as animals not operated upon, were used as positive controls.

Fig. 5 shows the results of bilateral forearm amputation on linear growth of the animal. A total of 14 experimental and 11 control animals were used. Note that, in the first 10 days while the blastema is forming, linear growth of the two groups is parallel. During the second 10 days while differentiation is rapidly taking place, there is a highly significant increase in the growth rate of the regenerating animals. In the last 10 days when differentiation is complete, the growth rate returns to normal. It would appear then that the actual process of biochemical and morphologic differentiation which takes place during the second period in some way stimulates growth.

DISCUSSION

During the embryonic period tissue and organ differentiation proceed concomitantly with growth. It is important to attempt to separate these two phenomena and to explore the effects of one upon the other.

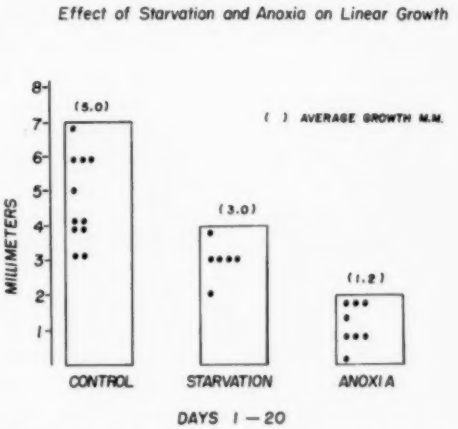

Fig. 3. Effects of starvation and anoxia on the growth of Ambystoma larvae. Each dot represents one animal.

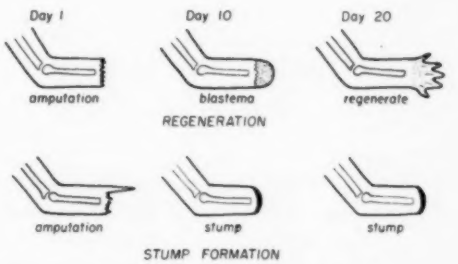

Fig. 4. *Upper,* Schematic diagram of the process of limb regeneration. *Lower,* Method of preventing regeneration by leaving a skin flap.

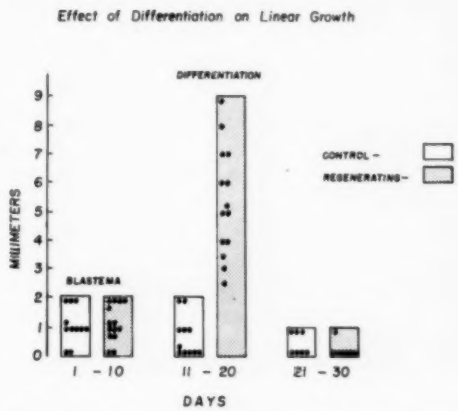

Fig. 5. Effect of differentiation on the linear growth of Ambystoma larvae. Each dot represents one animal.

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Holtfreter[7] has demonstrated that raising early frog embryos in an agar medium which physically prevented them from growing in size did not prevent differentiation from proceeding at a normal rate. It has been shown here that anoxia and starvation have similar effects in the larval period. These observations lead to the conclusion that embryonic growth may be delayed without affecting differentiation.

The experiments with limb regeneration were undertaken to examine the effect of tissue differentiation on growth. The results here indicate that the biochemical and morphologic events which take place during tissue and organogenesis in some manner stimulate linear growth. There is also evidence that specifically inhibiting differentiation retards growth.[8]

When both sets of experiments are combined, the possibility arises that the extremely complex process of embryonic differentiation, in addition to forming specialized tissues and organs, in some manner provides a growth stimulus to the embryo. Since very little is known at present about the mechanism of embryonic growth, further experiments appear to be warranted to define the exact nature of this growth stimulus.

SUMMARY

It has been demonstrated in the embryonic system of the salamander *(Ambystoma opacum)* that anoxia and starvation retard growth without retarding differentiation and that anoxia is the more potent agent. Tissue and organ differentiation, on the other hand, stimulate growth. The precise nature of this inherent stimulus awaits further study.

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Ear studies in the newborn infant

II. Age of spontaneous visibility of the auditory canal and tympanic membrane, and the appearance of these structures in healthy newborn infants

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PREVIOUS investigations showed that the auditory canal of the newborn infant less than 24 hours old is obscured by debris, presumably vernix caseosa.[1] Cleansing methods and the appearance of the cleansed canal and tympanum were described.[1] The present studies indicate the time and frequency of natural changes which permit otoscopic examination without cleansing, as well as further descriptions of the canal and ear drum during the first week of life.

PROCEDURE

Examinations on 524 occasions of the ears of approximately 250 healthy full-term infants were conducted in the hospital nursery; a few serial examinations were included. The ages of the infants ranged from 24 hours to 1 week (Table I); most of the infants were Negro. Rigid nursery techniques were observed. A Welch Allyn otoscope with fresh batteries was used; the infant-sized speculum was satisfactory in most instances, although the No. 208 speculum was necessary for a few infants with small canals.

The terminology and mode of quadration of the tympanic membrane used by previous authors[2-6] were followed and adapted to the supine infant. MacKenzie's descriptions[6] were especially valuable. Attempts were made to correlate physical appearances with anatomic studies of postmortem ear sections; these studies will be reported later.

RESULTS

Visibility. One hundred ninety-one ear canals and drums were satisfactorily visible at 524 examinations during the first week of life (Table I). It is to be noted that spontaneous visibility is infrequent until the fourth day of life. By the fifth day one-half of the ears are visible, and at 1 week 60 per cent. By "spontaneous visibility" is meant adequate visualization of the canal and drum by otoscopy without cleansing. In these instances, the long and short processes of the malleus, the cone of light, the color of the tensa and flaccida, and the hairy part of the canal could be seen. The observations

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Table I. Incidence of spontaneous visibility by age at 524 ear examinations

	*Age (days)**						
	1	*2*	*3*	*4*	*5*	*6*	*Total*
Drums and canals visible	0	3	19	78	49	42	191
Drums and canals not visible†	14	77	95	76	43	28	333

*Day of birth not counted.

†Includes 20 serial examinations.

in 51 ears consecutively found visible are presented in Tables II and III.

Canals. The appearance of the canals was much as described for the cleansed ears of the neonate.[1] Hairs were present, the crown wall was relatively short and straight, the caudal wall was longer and curved; the sagittal section was oval at the level of the ridge on the caudal wall. The junction of the canal with the drum is obtuse at the crown wall, where it is most readily seen; at the caudal wall the angle is acute. Anatomic studies confirmed these observations. They also showed that the bony canal is not developed, that the dorsal and ventral walls are folded inward and obscure the tympanic membrane from view, and that the caliber of the canal diminishes lateral to the tympanum. The skin of the canal sometimes appeared oily but was free of moisture and odor.

Debris. A certain amount of debris was present in the ears of most infants at 3 to 6 days of age, but it was in striking contrast to the creamy white or slightly yellow vernix caseosa which filled the canals or covered canal walls and drum during the first 24 hours of life.[1] A small amount of vernix was present in 15 of the 51 observations recorded in Table II, most often in a small pile near the ridge of the caudal wall. In 39 of the 51 examinations, a pale, grayish-yellow or brown material was caught in the speculum tip or was seen on the caudal or crown wall. Patches of dark-pigmented debris were sometimes seen on the tensa in Negro infants, and occasionally small flecks of dry blood were observed. No wax of the adult type was noted. Soft canal debris sometimes stuck on hairs in the field of vision, especially after repeated insertion and withdrawal of the speculum,[7] but it rarely obscured the drum.

Microscopic sections of flakes of debris from these ears, of vernix caseosa, and of newborn skin[8] all showed keratinized epithelium. Casual observation apart from this study indicated that birth debris may persist for several weeks in the ears of some infants.

Table II. Incidence of major physical findings on examination of 51 consecutive spontaneously visible ears in 32 newborn infants averaging 4.5 days of age

Observation	*No. of ears*
Vernix	15
Wax	0
Yellow debris in speculum tip	39
Hairs in canal	51
Color of tensa	
Pink	9
Gray	42
Color of flaccida	
Red	3
Pink	20
Gray	28
Cone of light	45
Ossicles	
Long	45
Short	51

Table III. Incidence of certain additional findings visible in the 51 ears from Table II

Observations	*No. of ears*
Tensa	
"Fireballs"	
Anterior	42
Posterior	34
Spokelike markings	33
Discrete vessels	28
Flaccida	
Discrete vessels	40
Dorsal gray area	45

Tensa. The pars tensa (Fig. 1) lay caudal and medial to the pars flaccida. Its lateral surface was concave and, caudal to the umbo in the area of the cone of light, the concavity was marked and seemed to be cylindrical. The surface color was more often gray (Table II) and less often pink than in the neonate at 24 hours of age.[1] The incus and other middle ear structures were rarely identified on otoscopic examination, but several special features, spokelike markings, cone of light, "fireballs," and blood vessels (Table III), will be discussed later.

Umbo. From the umbo, centered at the apex of the tensa, there seemed to radiate the manubrium, the tensa vessels, spokelike markings, and the cone of light (Fig. 1). The homogeneous, pale gray, circular area at the umbo, a landmark which is frequently present in children,[9] was seldom identified in the newborn.

Cone of light. This was visible in 45 of the 51 consecutive observations (Table II). It was more readily visible than in the cleansed ears of neonates at 24 hours[1] but smaller and less brilliant than in older children (Fig. 2). The cone occupied a small portion of the concave tensa between the umbo and the caudal wall, and was usually white or grayish in color. Small vessels often traversed the cone in a crown-rump direction. A thin film of debris, if present, dimmed the cone and produced a granular appearance.

Manubrium. The long process of the malleus, or manubrium, was identified in 45 of the 51 recorded observations (Table II). Occasionally the bone was seen, but more often a contrast of color and contour identified this structure. Foreshortening seemed less marked than in the infant at 24 hours.[1]

"Fireballs." Two luminous points on the tensa, not reported in the literature, were noted in most instances (Table III). Located ventral and dorsal to the umbo (Figs. 1 and 2), their glowing red color in the crying infant suggested the descriptive term "fireballs." In the quiet infant they were silvery white, pale yellow, or pink. They are present in premature as well as term infants and persist to the age of several months; in older children small shiny areas have been seen in the same location.

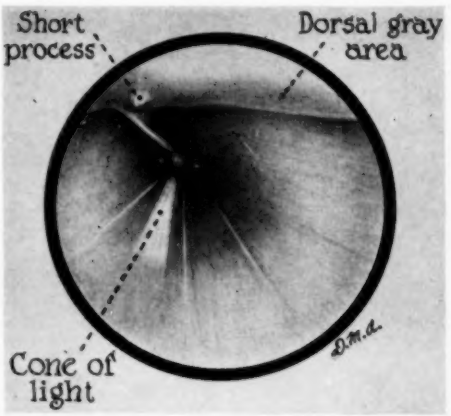

Fig. 1. Left ear drum as seen through speculum in first week of life (semidiagrammatic). Note small circular fireballs on each side of the umbo, also radiating spokelike markings dorsal and ventral to the cone of light.

These luminous points were small but varied in size, up to the size of the short process. They varied from circular to flame shaped or diffuse, but did not coalesce. They did not shift with movement of the light source, seeming to be less superficial than the cone of light, but they have not been explained by serial sections or other anatomic studies.

Spokelike markings. One to several hair-width lines radiated in spokelike fashion from the umbo toward the drum periphery on either side of the cone of light (Fig. 1). Some were white and slightly raised but less often they were indistinct and produced a ribbed effect on the tensa surface. Blood vessels were occasionally seen nearby, but were small and less prominent.

Short process. This structure was well illuminated and always identifiable in the crown-ventral sector near the canal wall (Fig. 1). Usually white or grayish, occasionally pale amber or pink, its color was little affected by crying. It was peaked, circular, and, under otoscopic magnification, appeared the size of a pinhead. The observation that blood vessels rarely coursed over its

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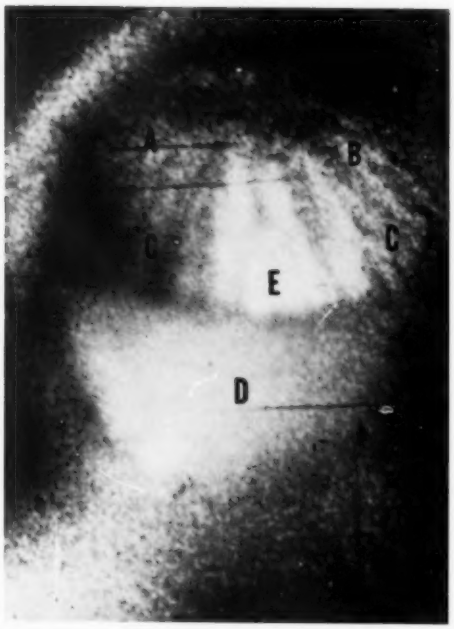

Fig. 2. Actual photograph of the ear of the newborn. *A, B,* Fireballs; *C, C,* spokelike markings; *D,* caudal canal wall; *E,* cone of light; horizontal lines, artifacts. From color photograph courtesy Dr. Jim Rutledge.

surface was confirmed by microscopic sections in autopsy studies.

Pars flaccida. This segment of the drum lay crownward to the short process. The anterior malleolar fold described by MacKenzie[6] was sometimes found, but the posterior fold described by him was not. The flaccida was less often red than in cleansed ears at 24 hours,[1] usually being pink or gray (Table II). Discrete vessels were seen in 40 of the 51 ear drums examined consecutively (Table III). Spontaneous movement of the flaccida was observed only 2 or 3 times; crying, sucking, or obstruction of the nares rarely produced any observed movements.

Dorsal gray area. A homogeneous gray area (Fig. 1) lies dorsal to the vascular area of the pars flaccida. Blood vessels were inconspicuous and spokelike markings were absent. It appeared to be thinner and less opaque than other portions of the drum; its color was not influenced by crying. It is assumed that this is part of the flaccida.

DISCUSSION

The desirability of examining the ears as a part of a complete examination of the newborn infant should be obvious. The occurrence of otitis media in the newborn[10] and the frequency of otitis media in autopsy studies of premature infants to be reported by one of us (M. S. M.) emphasize the importance of otoscopy.

We have previously shown[1] that the ear canals of neonates in the first 24 hours of life are obstructed by vernix, and that ether is an efficient cleansing fluid. The present study demonstrates progressive clearing of this obstruction during the first 72 hours, presumably as a consequence of general neonatal dehydration, to the point of spontaneous visibility of half or more of ear drums at 4 to 6 days of age. Cerumen, the chemical composition of which has been reported to be similar to that of vernix,[11] is not produced at this age.

Good instruments are essential; they include an otoscope with fresh batteries and an infant speculum. We consider examination with a head mirror inadequate because it does not show details which otoscopic magnification makes possible.

It is hoped that the landmarks which we have described—"fireballs," spokelike markings, and the dorsal gray area—may be potentially useful in delineating congenital abnormalities or disease states in the ears of the newborn. We have considered cartilage cell rests, unusually arranged connective tissue fibers, or variations in other tissues as the structural basis for the "fireballs," but as yet have no satisfactory explanation.

SUMMARY

In 524 examinations of ears during the first week of life in healthy full-term infants, 191 ears were adequately visualized without cleansing. The progressive spontaneous clearing of vernix is evidenced by the finding of 169 visible drums in 316 examinations (53.5 per cent) of newborn

infants on their fourth to sixth days of life, compared to only 22 visualizations in 208 examinations (10.5 per cent) in the first 3 days of life.

The normal landmarks in the immediate postnatal period are described. Ear drums become less reddened after the first 24 hours and landmarks become clearer, but the ear drums are pinker and the landmarks less distinct than in the older child.

New features described are the dorsal and ventral "fireballs," spokelike markings, and a dorsal gray area.

We are pleased to acknowledge the assistance and advice of many individuals in the course of this study. We express particular thanks to Dr. W. S. Harmon, Superintendent, and the resident, intern, and nursing staffs of Confederate Memorial Hospital; to Dr. W. R. Mathews, Director, Department of Pathology, and to Drs. Brown, Cummings, and Rondeau of the Pathology staff. Drs. L. J. Rutledge, B. D. Clem, and R. J. Platou, of Tulane University School of Medicine, gave factual and editorial advice.

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Dental caries experience of school children in Corvallis, Oregon, after 7 years of fluoridation of water

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THE high susceptibility to dental caries of children living in certain regions of the State of Oregon has been demonstrated.[1, 2] One of the geographic areas where the residents were shown to have a high incidence of caries is the Willamette Valley,[1-3] located in western Oregon between the Coastal and Cascade Ranges.

In January, 1953, Corvallis, a community in the Willamette Valley, had the municipal water fluoridated. The amount of fluoride in the water was 0.1 ppm[4] before its concentration was adjusted to 1.0 ppm in January, 1953. This amount has been recognized as optimum in temperate climates for reducing dental caries susceptibility, yet this concentration is low enough to prevent any but isolated instances of dental fluorosis, as demonstrated by the epidemiologic studies of Dean, Arnold, and Elvove.[5]

The purpose of this study was to investigate the effect of 7 years of fluoridation on the teeth of Corvallis school children.

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EXPERIMENTAL METHODS

Fluoride feed equipment. Volumetric feeders were installed in the two plants serving the community. Sodium fluoride was used in one plant, sodium silicon fluoride in the other until 1957, when both plants continued with sodium silicon fluoride as the sole source of the fluoride ion.

Selection of subjects.

Base-line study. In 1952, as a base-line pre-fluoridation project, Hadjimarkos[6] examined 1,534 Corvallis elementary school children ranging in ages from 5 to 12 years. This included all available children, regardless of previous residence.

Present study. During November and December, 1959, seven years after the initiation of fluoridation, 1,129 Corvallis school children were examined. The children were grouped as follows: (1) all available boys and girls, 12 to 17 years old on their last birthday, examined in 1952, who had used the municipal water supply since fluoridation was initiated and who had been absent from the area not more than 3 months in any year since then, and (2) all available boys and girls, 5 to 12 years old on their last

birthday, born and reared in Corvallis, who had used the municipal water supply since birth and who had been absent from the area not more than 3 months in any year.

Dental examinations. Procedures used in the present study were similar to those of the prefluoridation project,[6] except that in the present study the senior author examined the children and recorded the findings.

To designate dental caries experience, the following symbols were used: DMFT (decayed, missing, and filled teeth; teeth indicated for extraction were included in the designation of missing teeth), DT (decayed teeth), MT (missing teeth), and FT (filled teeth) for the permanent dentition; and deft (decayed teeth, teeth indicated for extraction, and filled teeth), dt (decayed teeth), te (teeth indicated for extraction), and ft (filled teeth) for the primary dentition.

Statistical analyses. Chi-square and "t" tests were used for all tests of hypotheses to determine statistical significance at the 5 per cent level of probability.

RESULTS AND DISCUSSION

The development of each permanent tooth covers a span of 10 years or more; therefore, a complete picture of the caries-inhibitory effect of fluoridation of water could not be observed after only 7 years. This has been demonstrated in a number of long-term studies with varying periods of exposure to fluoridated water.[7-10] Marked inhibition of dental caries activity, however, has been reported in various parts of this continent[9-15] in the seventh year after fluoridation of water was initiated.

In this study all the Corvallis children between the ages of 5 and 12 years examined for the first time were born and reared in the community. The boys and girls between the ages of 12 and 17 years who had been examined in the prefluoridation study were divided into two groups: (1) children born and reared in Corvallis, and (2) children born elsewhere who moved to Corvallis before 1952. No significant variation was found between the dental caries activity of the two groups of adolescents at any age level; therefore, they were combined into one group.

DENTAL CARIES EXPERIENCE BEFORE AND AFTER FLUORIDATION

Decayed, missing, and filled permanent teeth of children 12 to 17 years of age. The dental caries experience of all subjects examined 7 years after fluoridation was initiated is shown in Tables I and II and Fig. 1.

In the prefluoridation study the ages of the subjects ranged from 5 to 12 years. Seven years after fluoridation, all of the children still available were re-examined. They ranged in ages from 12 to 17 years. Only those children who were 5 years old in 1952, hence 12 years old in 1959, could be compared to the children 12 years of age in the base-line study. For these children, fluoridation of the water supply reduced the dental caries rates by 23 per cent from a mean of 6.82 DMFT to 5.23 DMFT, a statistically significant amount (Table III). This reduction in caries activity is comparable to that reported for the same age group and for approximately the same period of fluoridation by Hill, Blayney, and Wolf[9, 12] in Evanston, Illinois, the Division of Medical Statistics of the Ontario Department of Health in Brantford, Canada,[15] and Arnold, Dean, and Knutson[13] in Grand Rapids, Michigan. Pre- and postfluoridation caries rates of the subjects in Grand Rapids and in Corvallis are strikingly similar, as shown in Fig. 2.

Before fluoridation of the Corvallis water supplies, Hadjimarkos and Storvick[3] investigated the caries activity of permanent teeth of boys and girls, 14, 15, and 16 years old, born and reared in 5 Benton County communities. Because the majority of the subjects came from Corvallis and because environmental homogeneity exists, it seemed justifiable to compare the dental caries activity of this age group to the caries rates of the Corvallis children of the same age after fluoridation (Fig. 1). The mean caries rates of the Benton County children were 11.1 DMFT, 13.9 DMFT, and 14.6

Table I. Dental caries incidence in permanent and primary teeth of children, 5 to 17 years of age* 7 years after fluoridation of the Corvallis water supply was initiated†

Age		*Age when fluoridation was initiated*					*% of children without caries experience*		
In years, last birthday	*In months, since birth*	*In years*	*In months*	*No. examined*	*Mean DMFT per child*	*Mean deft per child*	*No DMFT*	*No deft*	*No DMFT and no deft*
5	60 to 71	0	In utero	101	0	3.13	100	37	37
6	72 to 83	0	9 (in utero to birth)	119	0.42	4.19	82	28	25
7	84 to 95	> 0	Natal, postnatal to 11	89	0.96	4.43	63	22	19
8	96 to 107	> 1	12 to 23	82	1.74	4.72	42	20	13
9	108 to 119	> 2	24 to 35	97	2.28	4.65	22	16	11
10	120 to 131	> 3	36 to 47	83	3.17	4.00	12	19	6
11	132 to 143	> 4	48 to 59	84	4.08	1.98	13	55	8
12	144 to 155	> 5	60 to 71	53	5.23	0.58	6	70	6
13	156 to 167	> 6	72 to 83	96	6.02	0.14	5	91	5
14	168 to 179	> 7	84 to 95	87	7.70	0.05	5	98	5
15	180 to 191	> 8	96 to 107	91	10.04	0.02	3	98	3
16	192 to 203	> 9	108 to 119	88	11.07	0	0	100	0
17	204 to 215	>10	120 to 131	59	12.64	0.02	2	98	0

*November-December, 1959.

†January, 1953.

DMFT at 14, 15, and 16 years of age, respectively. The mean caries rates of the Corvallis children of this age group after fluoridation were 7.7 DMFT, 10.0 DMFT, and 11.1 DMFT, respectively, reductions of 31, 28, and 24 per cent, and of 27 per cent for the three age groups combined. Arnold, Dean, and Knutson[13] reported similar reductions in dental caries activity for children of the same age group in the seventh year of fluoridation in Grand Rapids (Fig. 2). Even though the reduction of DMFT rates of this age group in Corvallis was not statistically significant, the reduction in tooth morbidity was. It was 60 per cent for the number of decayed teeth and 83 per cent for the number of missing teeth.

The dental caries experience of the children from the ages of 5 to 17 years was tabulated according to sex (Table II). Girls had a higher caries activity of their permanent teeth, boys of their primary teeth.

Decayed, missing, and filled permanent teeth of children 5 to 12 years of age. The dental caries rates of children ranging in ages from 5 to 12 years before and after fluoridation of the water supply are shown in Table III and Figs. 1 and 2.

Decayed, missing, and filled teeth. The permanent teeth of children 5 years (60 to 71 months) of age were not examined in the prefluoridation study.[6] During the postfluoridation survey, however, it was found that 7 children of that age had erupted permanent first molars and mandibular central incisors. All these teeth had been exposed to fluoridated water when tooth germ formation was initiated in utero, and all of them were found to be completely caries free.

All of the children who were 6 years old (72 to 83 months) had been exposed to fluoridated water since birth, the majority prenatally, and many at the onset of permanent tooth calcification.[16] The caries rates of their permanent teeth were 44 per cent less than the caries rates of the children of that age before fluoridation, a significant reduction. This reduction is comparable to the differences reported by Tank and Storvick[17] for children with lifelong exposure to water containing low or high concentrations of fluorides naturally, but less than that found by some of the investigators in fluoridated areas after 7 years of exposure.[9, 12-15] The reasons why the reductions, while signifi-

cant, seem to be less throughout the age ranges in this study than those reported in the other fluoridation studies may be the variability of diagnosis among different examiners.[18]

Even though the majority had only postnatal exposure to fluoridated water, children 7 years (84 to 95 months) of age showed a reduction in dental caries rates similar to that of the 6-year-olds (43.5 per cent). This demonstrates a significant postdevelopmental effect on erupted first molars and incisors.[19]

Percentage reductions in caries activity, highest when teeth had been exposed to fluoridated water during their development, declined with increasing age and increasing numbers of teeth which erupted in the prefluoridation period. At all ages, nevertheless, reductions were statistically significant when compared to the base-line data. This finding substantiates the reports of Russell[20] and those of other investigators[7-15] who found that fluoride, even when incorporated into tooth structure during calcification and after eruption of teeth, effectively reduces the susceptibility to dental caries. In this study, for children 8, 9, 10, 11, and 12 years old, the reduction in dental caries activity was 36, 40, 26, 21, and 23 per cent, respectively, and 34 per cent for all children from the ages of 6 to 12 years combined.

Beneficial effect of fluoridation became even more apparent from separate data on decayed teeth, missing teeth, and filled teeth (Table III).

Decayed teeth. Compared to the base-line values, fluoridation effected a progressive and statistically significant reduction of decayed permanent teeth with advancing age, until, at the age of 12 years, the children had a mean of 1.04 DT compared to a mean of 3.63 DT before fluoridation, a reduction of 71 per cent. For all the age groups combined, almost 3 times as many of the permanent teeth were found to be decayed before fluoridation (1.81 mean DT) as after fluoridation (0.64 mean DT), a significant reduction of 65 per cent.

Missing teeth. The Corvallis children had fewer teeth missing and indicated for extraction before fluoridation[6] than comparable age groups examined by Arnold, Dean, and Knutson[13] and by Tank and Storvick[21] in low fluoride areas of Wyoming (Table III). Even so, after fluoridation, statistically significant reductions occurred from a mean of 0.08 MT before to a mean of 0.01 MT after fluoridation, a decrease of 88 per cent. No permanent teeth had been extracted, nor were indicated for extraction for children 5, 6, 7, 8, and 10 years old after fluoridation, and means of only 0.01 MT per child for the 9- and 11-year-olds and 0.11 MT for the children 12 years of age were found. These reductions are greater than those observed in Grand Rapids[13] in the seventh year of fluoridation.

Filled teeth. An important effect of fluoridation was found in the increasing proportion of teeth filled to teeth untreated and missing (Table III). Similar observations were made by Arnold, Dean, and Knutson[13] and Ast and Chase[14] in the seventh year of fluoridation. In this study, the percentages of filled teeth after fluoridation increased for the ages of 7, 10, 11, and 12 years and for all ages combined and was statistically significant for the ages of 7, 10, and 11 years with increases of 20, 14, and 22 per

Table II. Dental caries incidence in permanent and primary teeth of children, 5 to 17 years of age, 7 years after fluoridation of the Corvallis water supply was initiated

Sex	*No. examined*	*Mean DMFT per child*	*Mean deft per child*	*% of children without caries experience*		
				No DMFT	*No deft*	*No DMFT and no deft*
Boys	528	4.01	2.52	34	53	13
Girls	601	5.24	2.10	28	58	10
Both sexes	1,129	4.67	2.30	31	56	12

Table III. Dental caries incidence in permanent teeth of children, 5 to 12 years of age, before fluoridation of the Corvallis water supply and 7 years after fluoridation was initiated

	Year of examination	*Age, last birthday*								
		5	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*All ages*
No. of children examined	1952	168	221	230	238	200	173	162	142	1,534
	1959	101	119	89	82	97	83	84	53	708
Mean No. of DMFT per child	1952	---	0.75	1.70	2.73	3.82	4.28	5.17	6.82	2.94
	1959	0.00	0.42	0.96	1.74	2.28	3.17	4.03	5.23	1.95
% difference†	1959		-44*	-44*	-36*	-40*	-26*	-21*	-23*	-34
Mean No. of decayed teeth per child	1952	---	0.62	1.39	1.80	2.58	2.49	2.99	3.63	1.81
	1959	0.00	0.39	0.52	0.78	0.82	0.89	1.04	1.04	0.64
% difference	1959		-37*	-63*	-57*	-68*	-64*	-65*	-71*	-65
Mean No. of missing teeth‡ per child	1952	---	0.00	0.01	0.03	0.13	0.16	0.14	0.29	0.08
	1959	0.00	0.00	0.00	0.00	0.01	0.00	0.01	0.11	0.01
% difference	1959		0	-100	-100	-92*	-100*	-93*	-62*	-88
Mean No. of filled teeth per child	1952	---	0.14	0.40	1.16	1.65	2.25	2.88	3.70	1.38
	1959	0.00	0.04	0.48	1.04	1.58	2.57	3.50	4.26	1.44
% difference	1959		-71*	+20*	-10	-4	+14*	+22*	+15	+4
Mean No. of DMF first molars per child	1952	---	0.75	1.67	2.61	3.19	3.40	3.47	3.58	2.26
	1959	0.00	0.40	0.94	1.73	2.16	2.93	2.85	3.32	1.61
% difference	1959		-47*	-44*	-34*	-32*	-14*	-18*	-7	-29
Per cent of children caries free (without DMFT)	1952	---	66	34	11	8	5	3	1	19
	1959	100	82	63	42	22	12	13	6	47
Per cent of children completely caries free (without DMFT and deft)	1959	37	25	19	13	11	6	8	6	17

*Significant at the 5 per cent level.

†Increase +, reduction −.

‡Includes teeth indicated for extraction.

cent FT, respectively. Two reasons may account for the increased proportion of filled teeth: (1) with fewer teeth decayed, the needs for dental care can be more easily met; and (2) parents and children are increasingly aware of the need for dental health, as a result of the fluoridation program in the community.

First permanent molars. The permanent teeth most susceptible to decay among children of the age group studied are the first permanent molars. This becomes evident when the numbers of DMF teeth and DMF first molars are compared (Table III). Reductions by fluoridation diminished with progressively diminishing periods of exposure of the first molars to fluoridated water, and ranged from 47 per cent at 6 years of age to 7 per cent at the age of 12 years and was 29 per cent for all ages combined. All reductions, except at age 12, were statistically significant. The considerable pre- and posteruptive caries inhibitory effect of fluoride on first permanent molars has also been demonstrated by other investigators.[5, 13, 14, 22]

Decayed primary teeth, teeth indicated for extraction, and filled primary teeth of children 5 to 8 years of age.

Decayed teeth, teeth indicated for extraction, and filled teeth. In the base-line study, only the primary teeth of the children from the ages of 5 to 8 years were studied.[6] In the postfluoridation study, the primary teeth of all boys and girls were examined (Table I and Fig. 1), but the comparison of caries

attack rates before and after fluoridation is limited to the age ranges examined in the prefluoridation study. Interestingly, it was found that the dental caries experience of the primary teeth of Corvallis children 5 to 13 years old very closely resembled the findings reported for Grand Rapids, Michigan,[13] before and in the seventh year of fluoridation, as shown in Fig. 2.

With exposure to fluoridated water from initial calcification, which according to a recent report by Kraus[23] may begin as early as the twelfth week in utero, to final calcification of crowns, roots,[16] and eruption of primary teeth, reduction in dental caries incidence regressed (Table IV, Figs. 1 and 2). In the postfluoridation study the highest caries activity among the children of all age groups occurred at the age of 8 years (Table I), while in the prefluoridation study the highest caries activity was reached at the age of 6 years (Table IV, Figs. 1 and 2). Reductions in dental caries rates of the primary teeth after 7 years of fluoridation were statistically significant for the 5-, 6-, and 7-year-old children and for all the age groups combined and were 30, 26, 21, and 23 per cent, respectively (Table IV). For the children 8 years of age, they were lower (11 per cent) and not statistically significant. Nevertheless, the considerable reduction in dental caries susceptibility at 7 and 8 years of age again demonstrates the marked effectiveness of exposure to fluoridation in the prevention of dental caries, even after calcification of crowns[16, 23] or the eruption of teeth.[24]

While the reductions in caries activity of the primary teeth of this age group were less pronounced than those found in Grand Rapids[13] and Brantford[10, 15] for approximately the same time of exposure, the reductions in Corvallis were considerably higher than those found in Evanston.[11, 12]

Decayed teeth. Water fluoridation markedly reduced the number of decayed primary teeth (Table IV). Reductions of carious teeth were statistically significant for

Table IV. Dental caries incidence in primary teeth of children, 5 to 8 years of age, before fluoridation of the Corvallis water supply and 7 years after fluoridation was initiated

	Year of examination	*Age last birthday*				
		5	*6*	*7*	*8*	*All ages*
No. of children examined	1952	168	221	230	238	857
	1959	101	119	89	82	391
Mean No. of deft per child	1952	4.48	5.67	5.60	5.32	5.32
	1959	3.13	4.19	4.43	4.72	4.08
% difference†	1959	-30*	-26*	-21*	-11	-23
Mean No. of decayed teeth per child	1952	2.61	3.38	3.04	2.48	2.89
	1959	1.50	1.28	1.04	0.93	1.21
% difference	1959	-43*	-62*	-66*	-63*	-58
Mean No. of teeth indicated for extraction per child	1952	0.01	0.20	0.30	0.23	0.20
	1959	0.01	0.03	0.04	0.05	0.03
% difference	1959	0	-85*	-87*	-78*	-85
Mean No. of filled teeth per child	1952	2.07	2.29	2.57	3.00	2.52
	1959	1.75	3.16	3.51	4.17	3.09
% difference	1959	-16*	+38*	+37*	+39*	+23
% of children caries free (without deft)	1952	22	11	11	11	13
	1959	37	28	22	20	27
% of children completely caries free (without DMFT and deft)	1959	37	25	19	13	24

*Significant at the 5 per cent level.

†Increase +, reduction −.

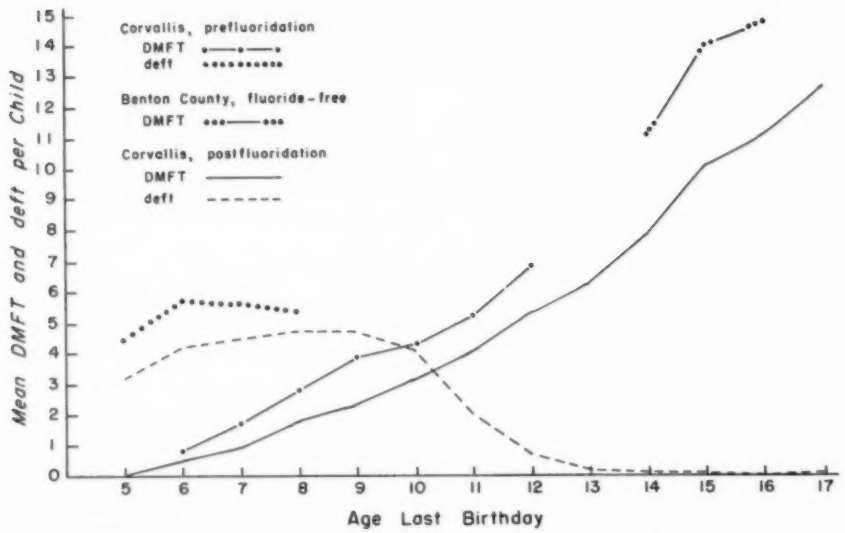

Fig. 1. Dental caries incidence of permanent teeth (DMFT) and of primary teeth (deft) of children before fluoridation of the Corvallis water supply and 7 years after fluoridation was initiated.

all age groups separately and were 43, 62, 66, and 63 per cent for the ages of 5, 6, 7, and 8 years. A reduction of 58 per cent for all ages combined shows that more than twice the number of teeth had open lesions before fluoridation, a mean dt of 2.89 before compared to 1.21 dt after fluoridation.

Teeth indicated for extraction. Statistically significant reductions in the number of primary teeth indicated for extraction were found after fluoridation, except in the 5-year-old children (Table IV). For all age groups combined, the number of teeth requiring extraction was less than one sixth of the number before fluoridation, a reduction of 85 per cent, or from a mean of 0.20 te to 0.03 te.

Filled teeth. As was true for the permanent teeth after exposure to fluoridation, as the number of primary teeth that were carious or indicated for extraction became less, more of the dental health needs were met (Table IV). With advancing age the proportion of teeth which had been filled increased significantly. For the 5-year-old children, there still was a reduction of filled teeth to the extent of 16 per cent over the prefluoridation period. But for the 6-, 7-, and 8-year-old children the number of filled teeth per child increased by 38, 37, and 39 per cent, respectively, after fluoridation.

Children without dental caries experience before and after fluoridation.

Boys and girls 5 to 17 years of age. After 7 years of fluoridation 31 per cent of all the subjects 5 to 17 years of age had permanent teeth without any past or present dental caries experience (Tables I and II). Boys and girls of this age span were not examined in Corvallis before fluoridation; therefore, comparisons cannot be made with Corvallis children. However, in a study on the caries activity of children born and reared in 5 western states, Tank and colleagues[2] found that 0.8 per cent of their subjects, 14, 15, and 16 years of age, were without past or present caries experience in fluoride-free areas as compared to 10 per cent in endemic fluoride areas. In the present study, 3 per cent of the children of the same age group had completely caries-free permanent dentitions after 7 years of fluoridation.

Twelve per cent of the Corvallis children from 5 to 17 years of age were without

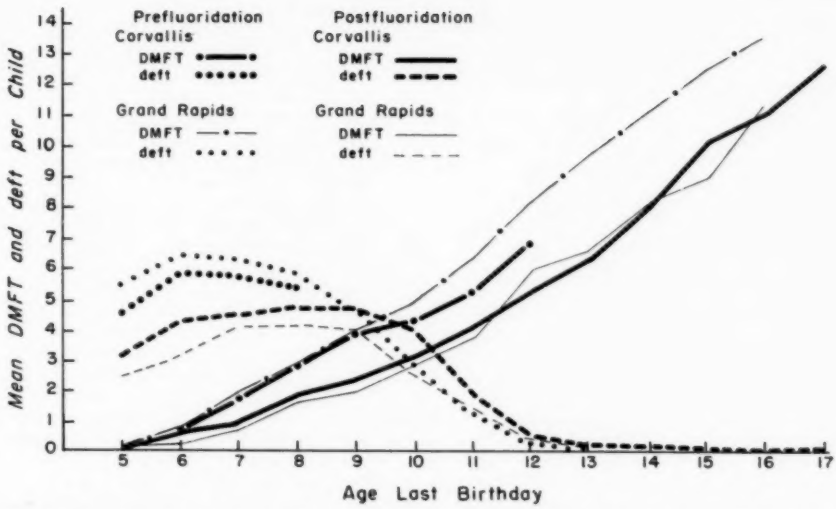

Fig. 2. Dental caries incidence of permanent teeth (DMFT) and of primary teeth (deft) of children before fluoridation of the Corvallis water supply and 7 years after fluoridation was initiated, compared to the caries incidence of Grand Rapids, Michigan,[13] children before fluoridation and after the seventh year of fluoridation.

caries experience of both permanent and primary dentitions after fluoridation. Hutton, Linscott, and Williams[10] reported that 5 per cent of their subjects in Brantford, Ontario, from the ages of 5 to 16 years were without DMFT and deft before and 19 per cent after 7 years of exposure to fluoridation. Primary teeth, however, were evaluated only to the age of 11 years. Tank and Storvick[21] found 1 per cent of their Wyoming subjects from the ages of 10 to 18 completely caries free (without DMFT and deft) in areas with 0.0 to 0.5 ppm of fluoride and 4 per cent in areas with 0.6 to 2.6 ppm of fluoride in the drinking water. In this study, 4 per cent of the children 10 to 17 years of age were found to have had no dental caries experience of their permanent and primary teeth after only 7 years of water fluoridation.

Boys and girls 5 to 12 years of age. Among the children from the ages of 5 to 12 years, more than twice as many children were free from past and present caries experience of their permanent teeth after fluoridation (47 per cent versus 19 per cent), as shown in Table III. Seventeen per cent had completely caries-free permanent and primary dentitions (no DMFT and deft) in 1959.

Boys and girls 5 to 8 years of age. The effect on primary dentition was similar to that noted on permanent dentition. Before fluoridation, 13 per cent of the children, ranging in ages from 5 to 8 years, had completely caries-free primary teeth (Table IV). After fluoridation the number of children without caries experience of the primary teeth was more than doubled and amounted to 27 per cent. Of that age group 24 per cent had completely caries-free primary and permanent teeth (no deft and DMFT) in 1959.

Hill, Blayney, and Wolf[11] reported differences in the percentages of children 6 to 8 years of age with completely caries-free primary dentitions before and after 6 and 8 years of exposure to fluoridation, which were considerably less than those found in the present study among children of the same age range.

SUMMARY AND CONCLUSIONS

Seven years after the adjustment of the fluoride content of the municipal water supply to 1.0 ppm, the dental caries experience

of elementary school children of Corvallis, Oregon, was investigated.

The following facts were determined:

1. Dental caries rates of the permanent and primary teeth for the children of ages 5 to 12 years were significantly reduced by 7 years of exposure to fluoridated water when compared to the caries rates of Corvallis children of the same ages who had been examined before fluoridation was initiated. A marked reduction in caries incidence also occurred in teeth which had developed before fluoridation of the water.

2. A significant reduction was shown in the number of decayed and missing permanent teeth, decayed primary teeth, and teeth indicated for extraction.

3. A marked increase in the number of filled permanent and primary teeth after fluoridation compared to the prefluoridation data was found.

4. Reductions in the number of decayed, missing, and filled first permanent molars became greater with progressively increasing periods of exposure of the teeth to fluoridated water.

5. After fluoridation, more than twice as many children were free from caries experience of the permanent or primary teeth as had been before fluoridation.

Although the maximum effects on the teeth of the children studied cannot be expected before 12 years of exposure to fluoridated water, the beneficial results which were apparent after only 7 years of fluoridation are highly significant.

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The use of kanamycin sulfate as a therapeutic agent for infants and children

An analysis of 140 cases treated during a two-year period

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KANAMYCIN SULFATE† was isolated from *Streptomyces kanamyceticus* by Umezawa in 1957. Early studies indicated that the drug was active against staphylococci, *Mycobacterium tuberculosis,* and many gram-negative pathogens. While initial clinical studies in Japan were in patients with pulmonary tuberculosis, during the last two years kanamycin has been used in this country in the treatment of a variety of acute bacterial infections in infants and children.

The advantages of the use of kanamycin in the treatment of pediatric patients are: its bactericidal mode of action, its wide spectrum of antibacterial activity, the low frequency of naturally occurring kanamycin-resistant strains of staphylococci, the frequency with which many strains of gram-negative bacilli are susceptible to its action, and its rapid absorption following intramuscular injection.

The antibacterial action of kanamycin is primarily bactericidal in that the concentration of the antibiotic required to kill bacteria is approximately equal to the concentration required to produce bacteriostasis.[1] Wise[2] states that the importance of the bactericidal activity of an antibiotic in therapy is not well understood since these effects are not commonly determined and, therefore, correlations are unknown. There is some clinical evidence, however, to suggest that there is a definite relationship between bactericidal activity and efficacy of therapy, particularly in patients with poor defense mechanisms and in patients with large numbers of infecting organisms. In the analysis of the management of 204 cases of staphylococcal disease in infants and children Yow, Desmond, and Nickey[3] demonstrated a lower mortality rate and a lower relapse rate with the use of bactericidal than with the use of bacteriostatic drugs. This point needs further clarification but bactericidal drugs seem to be indicated in the management of severe infections in young infants.

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Microbiologic studies reveal a wide spectrum of in vitro activity of kanamycin against the Staphylococcus, Vibrio, Salmonella, Shigella, Mycobacterium, the coliform group, and some strains of Proteus and Pseudomonas. Similar in vivo activity has been demonstrated and reported in numerous articles.[4, 5, 6] Disease states due to gram-negative bacilli and staphylococci constitute a major problem in the pediatric age group. This problem is especially great in the neonatal period when the infant has not only increased susceptibility to infection due to these two groups of organisms, but also the opportunity to acquire these infections in the hospital environment.

Gourevitch and co-workers,[7] using serial transfers of *Staphylococcus aureus* and *Escherichia coli,* have demonstrated that development of resistance to kanamycin in vitro occurs in a slow, stepwise fashion. Clinical experiences indicate that the development of resistance during treatment has not been a problem.

Kanamycin sulfate can be administered by the intravenous intramuscular, oral, and local routes. The intramuscular route is usually employed. Kanamycin is rapidly absorbed when injected intramuscularly, yielding peak serum concentrations within one hour. The drug is infrequently administered by the intravenous route since the intramuscular route is so satisfactory. Ordinarily only small amounts of kanamycin are absorbed from the gastrointestinal tract so that it cannot be given by this route to achieve systemic effect. It is given by mouth only for the purpose of altering gastrointestinal flora. It is noteworthy, however, that a recent study by Kunin and associates[8] demonstrates that patients with renal impairment and patients with cirrhosis of the liver complicated by renal failure have appreciable accumulative blood levels of kanamycin following oral administration of the drug. Kanamycin has been used locally for the treatment of superficial infections and for instillation into abscess cavities, the peritoneal cavity, pleural spaces, and the subarachnoid space.

The toxic effects reported following the use of kanamycin have been injury to the acoustic nerve, nephrotoxicity, mild maculopapular skin rashes, and transient eosinophilia.[7, 9, 10, 11] Most of the toxicity studies have been carried out on adult patients. The side effects of the drug when used for infants and children require further definition.

Kanamycin became available for clinical trial at Jefferson Davis Hospital, Houston, Texas, in December, 1957. Preliminary laboratory studies revealed this antibiotic to be highly bactericidal against a strain of *Staph. aureus,* phage type 42B/81/44A/70, which was the etiological agent responsible for a nursery outbreak at Jefferson Davis Hospital at that time. The severity of the illnesses in this outbreak and the high mortality rate with established methods of treatment made a trial of kanamycin advisable.

Experience with the use of kanamycin in the treatment of the infants involved in the nursery outbreak was so gratifying that the use of the drug was extended to older infants and children with infections due to

Table I. Age distribution and mortality rate of 140 children treated with kanamycin

Age	*No. of patients*	*Deaths*	*Percentage*
Newborn infants:			
Premature	30	18	60
Full term	68	8	12
Children 2 months to 2 years	32	5	16
Older children 2 to 14 years	10	2	20
Total	140	33	24

Table II. Major diagnosis in 140 patients treated with kanamycin

Site of infection	*No. of patients*
Gastroenteritis	49
Septicemia	30
Pneumonia	11
Pyoderma	11
Subcutaneous abscess	9
Deep abscesses	6
Osteomyelitis	3
Omphalitis	3
Thrombophlebitis	2
Miscellaneous	16
Total	140

Table III. Causative organism in kanamycin treated infections

Staphylococcus	78
Coliform group	33
Proteus	5
Beta streptococcus	1
Mixed or unknown	23
Total	140

staphylococci and to gram-negative bacilli. During the last two years we have treated a total of 140 children with kanamycin. The following article summarizes our experience with this drug.

DESCRIPTION OF CASES

Age distribution. The ages of the children in this study ranged from 12 hours to 14 years (Table I). There were 98 infants under 2 months of age, 32 from 2 months to 2 years of age, and 10 older children. The group under 2 months of age was comprised of 30 premature infants and 68 full-term babies. The weights of the premature infants ranged from 1,000 to 2,499 grams.

Forms of disease. The principal clinical diagnoses encountered in the 140 patients are listed in Table II. Many patients had infection of several organ systems but for the sake of simplicity only the major sites of involvement are listed. It should be emphasized that in the newborn infants staphylococcal disease tended to become widely disseminated with involvement of multiple systems. Septicemia was the most common diagnosis in the group of staphylococcal infections. In the patients with infection due to coliform organisms the gastrointestinal tract was the most frequently involved area. Sixteen patients are classified in Table II as having miscellaneous infections. Thirteen of the 16 presented the following diagnoses: otitis media 3, infected burns 2, infected wounds 2, urinary tract infection 2, meningitis 1, brain abscess 1, ethmoiditis 1, liver abscess 1. Three premature infants received kanamycin without a specific diagnosis because they were involved in a premature nursery outbreak of fulminating disease due to *E. coli* 0111:B_4.

One hundred and twenty of the children were seriously ill when kanamycin therapy was instituted. Ten of the infants were moderately ill. Ten were mildly ill but had a potentially serious infection. Approximately one-half of the 140 children treated with kanamycin had failed to respond to other antibiotic therapy before kanamycin was administered (Figs. 1 and 2). The majority of these children were critically ill when kanamycin was started, and many were moribund.

Description of causative organisms. A specific bacteriologic diagnosis was established in 117 of the 140 patients treated with kanamycin (Table III). In the 23 cases the etiological agent could not definitely be established because of the presence of mixed flora. There were 78 cases of infection due to *Staph. aureus,* 33 to organisms of the coliform group, 5 to Proteus species. Of the 33 infections due to coliform organisms, 28 of the etiological agents were pathogenic serotypes of *E. coli* and 5 were strains of *Klebsiella pneumoniae.*

The sensitivity to kanamycin of 50 of the causative organisms was determined by the tube dilution method as performed by Gourevitch.[7] The remaining organisms were tested by the standard disc technique with the use of 1, 5, and 30 mcg. per milliliter discs. The "epidemic strain 81" staphylococcus of the nursery outbreak was inhibited by less than 6.5 mcg. per milliliter of kanamycin. This strain was resistant to penicillin, streptomycin, erythromycin, and the tetracyclines. The miscellaneous strains of *Staph. aureus* isolated from the older infants and children were also uniformly inhibited by kanamycin concentrations of less than 6.5 mcg. per milliliter. There was, of course, less uniformity in their resistance to other antibiotics. One of the strains of *E. coli,* tested by the tube dilution technique, was inhibited by 12.5 mcg. per milliliter. The other 27 strains were tested by the disc technique and showed an inhibition zone around the 5 mcg. per milliliter disc. All 5 strains of Proteus species were inhibited by 30 mcg. per milliliter, 4 by 5 mcg. per milliliter, and none by

1 mcg. per milliliter. The 5 strains of *K. pneumoniae* were inhibited by 6.5 mcg. per milliliter of kanamycin.

Dosage of kanamycin. Kanamycin was given by the intramuscular route in doses of 10 to 100 mg. per kilogram per day. The intervals between doses were 6, 8, and 12 hours. When the larger doses, 50 to 100 mg. per kilogram per day, were used, the drug was administered in 4 divided doses. Daily amounts of 30 to 50 mg. per kilogram per day were divided into 3 doses and below 25 mg. per kilogram per day into 2 doses. During the first few months of using kanamycin a wide range of dosage, 10 to 100 mg. per kilogram per day, was used. During the second year clinical trial indicated that the range of 12.5 to 50 mg. was satisfactory. There was no evidence to suggest that doses larger than 50 mg. per kilogram per day had any added therapeutic advantage. In most cases the regimen used was 50 mg. per kilogram per day until clinical improvement occurred; then 25 mg. until the patient became asymptomatic; and 12.5 mg. thereafter for a variable length of time depending upon the nature of the infection. In premature infants, and in other individuals with altered renal function, 25 mg. per kilogram per day was usually selected as the initial dose for severe infection.

Kanamycin solutions (2.5 mg. per milliliter) were used for local instillation into the thoracic cavity, for irrigation of wounds and joint spaces and as intrathecal medication.

Kanamycin was the first drug used in the management of 73 of the 140 patients, either singly or in combination with another antibiotic. In 67 instances it was used after patients had failed to respond during an adequate trial period of treatment with other antimicrobial agents. The drug most commonly employed simultaneously with kanamycin was penicillin. It was generally used during the first 48 hours of kanamycin treatment. When the etiological agent and its sensitivity to kanamycin was established, penicillin was discontinued.

The duration of kanamycin therapy depended upon the severity of the infection, the site of the infection, and the adequacy of drainage. In general, superficial skin infections were treated for approximately 7 days, subcutaneous abscesses for 10 to 14 days, septicemia without known localization of infection in the viscera for 21 days, gastroenteritis for 14 days. Patients with pneumonia received the longest and most intensive therapy. The minimum length of therapy was fixed at 21 days on the basis of the findings of Disney and his associates.[12] Most of the children with pneumonic involvement received kanamycin for 4 to 6 weeks. The longest course of kanamycin therapy, 95 days, was administered to a boy with chronic osteomyelitis. Two other children received kanamycin for 54 and 45 days. One of these children was being treated for staphylococcal meningitis and the other for multiple pyogenic liver abscesses.

Table IV. Patients with staphylococcal infections treated with kanamycin

Diagnosis	*No. of patients*	*Recovered*	*Unimproved*	*Deaths due to infection*	*Deaths due to other causes*
Septicemia	21	10		9	2
Gastroenteritis	13	10	1	2	
Pyoderma	10	10		0	
Subcutaneous abscess	11	11		0	
Pneumonia	5	3		2	
Osteomyelitis	3	2	1	0	
Abdominal abscess	3	2	1	0	
Otitis media	3	1	2	0	
Omphalitis	3	3		0	
Meningitis	1			1	
Brain abscess	1			1	
Miscellaneous	2	1		0	1
Thrombophlebitis	2	2		0	
Total	78	55	5	15	3

RESULTS

In order that the analysis of the results of the management of this large number of children of different ages with different types of infection may be more meaningful, the results have been tabulated by etiological agents.

Staphylococcal infections. Table IV presents the results of treatment of 78 patients with staphylococcal disease. Fifty-five of the children recovered completely, 5 were unimproved, and 18 died. The greatest number of deaths was in the septicemia group. All of the children who succumbed to staphylococcal septicemia were newborn infants and the majority of these were born prematurely. The 2 deaths due to staphylococcal gastroenteritis also occurred in newborn babies. At autopsy each of these babies had perforating abscesses of the gastrointestinal tract. The 2 children who died of pneumonia had an accompanying empyema which was not adequately drained. Three patients died of causes unrelated to infection.

Escherichia coli infections. Twenty-four patients were treated for serious infections due to *E. coli* (Table V). Seventeen of them recovered and 7 died. Only 4 of the deaths were related to infection. Eighteen of the children with *E. coli* infections were premature infants involved in a nursery outbreak of gastroenteritis due to *E. coli* 0111:B_4. Three small premature infants died from infection very early in the course of their disease, 13 recovered, and 2 died from congenital anomalies.

Klebsiella infections. Five patients presented with klebsiella infections, 3 with pneumonia, and 2 with septicemia (Table VI). There were 4 recoveries and one death in this group. The death occurred in an infant who had a chronic debilitating disease and had been treated with multiple antibiotics. Postmortem examination of this infant revealed a large walled-off abscess in the upper lobe of the left lung. There were viable Klebsiella organisms within the abscess cavity.

Proteus infections. The results of kanamycin treatment in the five patients with proteus infection were very satisfactory (Table VII). Four children recovered. One 10-year-old boy had an abscess involving the posterior wall of the bladder following a traumatic rupture of the bladder. He failed to respond to therapy with multiple anti-

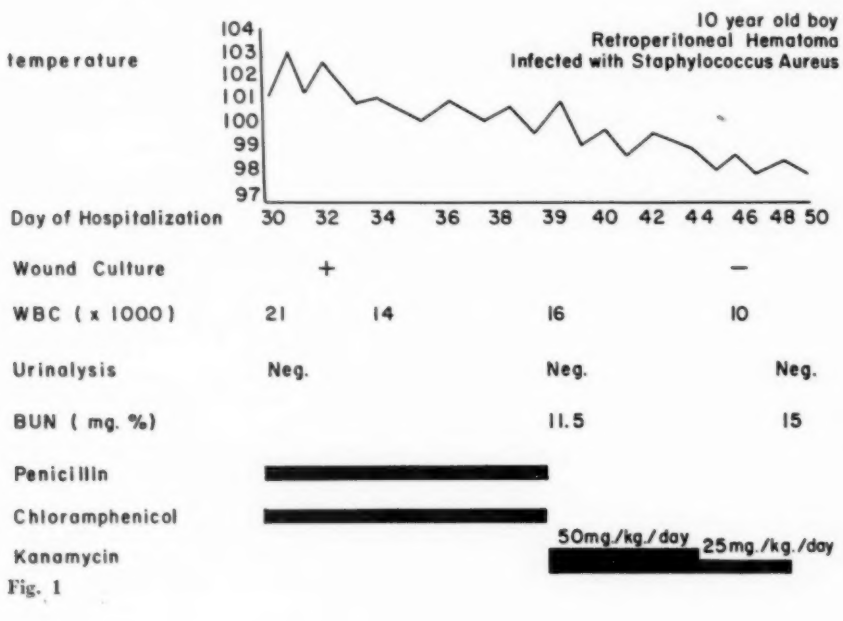

Fig. 1

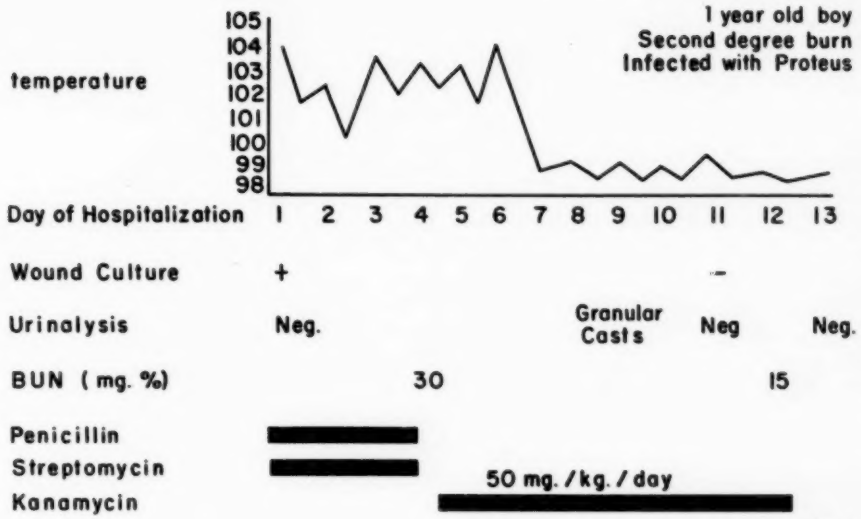

Fig. 2

biotics but responded dramatically to kanamycin. The patient with chronic otitis media which did not improve on kanamycin treatment failed to benefit from other antimicrobial therapy until a mastoidectomy was performed.

Mixed infections. Results of the management of 20 of the 23 patients with mixed infection or infections of unknown etiology are presented in Table VIII. Gastroenteritis was the anatomic diagnosis in 17 infants under 2 months of age. Nine of these children recovered, one was unimproved, and 7 died. Postmortem findings revealed death to be due to causes unrelated to infection in 4 of 7 total cases. Two children with pneumonia and one with pyoderma had a complete recovery.

Analysis of deaths. In the entire group of 140 patients treated with kanamycin there were 33 deaths (Table I). The mortality rate of 60 per cent in premature infants was significantly higher than in full-term newborn infants or in older children. The 12 per cent mortality shown for full-term newborn infants is unusually low because of the inclusion of 10 mildly ill infants in this group. The death rates of the infants from 2 months to 2 years of age and that of older children are comparable since all of these children were severely ill.

Table IX lists the causes of death—late institution of therapy, overwhelming infection, inadequate dosage of kanamycin, inadequate drainage, and death from causes unrelated to infection.

TOXICITY

Side effects associated with kanamycin therapy were difficult to assess. During the first year of kanamycin usage the renal status of the patients was evaluated very carefully. Blood urea nitrogen values were obtained prior to, and twice weekly during, the course of treatment. Urinalyses were performed prior to treatmen., on alternate days during kanamycin therapy, and several days post therapy. Most of the seriously ill patients had elevated blood urea nitrogen values, albuminuria and, cylindruria prior to the use of any drug. In general, the blood urea nitrogen returned to normal and the albuminuria disappeared as the patient's state of hydration improved. The cylindruria usually cleared but tended to occur intermittently during the course of kanamycin therapy, especially in patients receiving doses of 50 to 100 mg. per kilogram per day. Albuminuria was not related to kanamycin therapy and in no instance could elevation of the blood urea nitrogen be definitely related to the drug. As it became evident that

Table V. Patients with Escherichia coli infections treated with kanamycin

Diagnosis	*No. of patients*	*Recovered*	*Deaths due to infection*	*Deaths due to other causes*
Gastroenteritis	18	13	3	2
Septicemia	2	1	1	
Pneumonia	2	1	0	1
Deep abscess	1	1	0	
Subcutaneous abscess	1	1	0	
Total	24	17	4	3

Table VI. Patients with Klebsiella pneumoniae infections treated with kanamycin

Diagnosis	*No. of patients*	*Recovered*	*Deaths due to infection*	*Deaths due to other causes*
Pneumonia	3	2	1	0
Septicemia	2	2	0	0
Total	5	4	1	0

Table VII. Patients with Proteus infection treated with kanamycin

Diagnosis	*No. of patients*	*Recovered*	*Unimproved*	*Deaths*
Infected burn	2	2		0
Omphalitis	1	1		0
Abscess of bladder wall	1	1		0
Otitis media	1		1	0
Total	5	4	1	0

Table VIII. Patients with infections of unknown etiology treated with kanamycin

Diagnosis	*No. of patients*	*Recovered*	*Unimproved*	*Deaths due to infection*	*Deaths unrelated to infection*
Gastroenteritis	17	9	1	3	4
Pneumonia	2	2		0	0
Pyoderma	1	1		0	0
Total	20	12	1	3	4

nephrotoxicity was not as serious a problem as anticipated, urinalyses and blood urea nitrogen values were obtained at less frequent intervals. The management of patients treated during the last year included examination of the urine prior to treatment and twice weekly during treatment. A blood urea nitrogen determination was obtained prior to treatment and at weekly intervals during treatment. Renal toxicity did not necessitate the discontinuation of kanamycin in any of the children treated at Jefferson Davis Hospital.

Eighth nerve toxicity was not observed in this group of patients; however, the ages of the children in the study made evaluation of this problem difficult. In the older children no gross hearing loss could be detected. Three patients aged 2, 4, and 7 years received large doses of kanamycin for a duration of 45, 54, and 95 days, respectively. One year after kanamycin therapy all 3 of these children have normal hearing on audiometric testing. Hearing evaluation tests are now being performed on the younger infants and children who have reached at least 18 months of age. Results of these studies will be published at a later date.

DISCUSSION

After two years of experience with the use of kanamycin in the treatment of severely ill

infants and children, we feel that it is a valuable drug for the management of hospitalized pediatric patients. This conclusion was drawn not only from the data presented in this paper but also from the change in the mortality rate in a staphylococcal outbreak from 51 to 26 per cent following institution of kanamycin therapy. This change in mortality was attributed principally to the specificity of the drug for the etiological agent in this outbreak but, of course, was also influenced by a growing awareness of the nature of the disease in the outbreak. This awareness resulted in earlier diagnosis and treatment. The over-all mortality rate in the group of 140 patients presented here was 24 per cent. Although the mortality rate appears high, two factors caused this study to constitute an unusually severe test for the efficacy of kanamycin; the age of the patients and the severity of their illnesses. Seventy per cent of the patients were less than 2 months of age and 20 per cent weighed less than 2,500 grams. It is well established that both the full-term infant and the premature infant have an altered response to infection resulting in a higher mortality rate than that in the older child. The mortality rate in the premature infants was three times that in older infants and children. Most of the patients in this study were severely ill. The severity was due not only to the nature of the infecting organisms but also in many instances to the progression of the disease process to the point of irreversible tissue damage to vital structures before kanamycin was instituted. The morbidity and relapse rates were thought to be considerably less in the kanamycin-treated infants than in similar patients with comparable disease treated with bacteriostatic agents during the last two years.

The antibacterial spectrum of kanamycin makes it valuable in the treatment of infants and children who have infections due to a wide range of microorganisms. It is especially useful in the early management of severe infections of the newborn. The majority of infections in newborn children are now due either to hospital strains of staphylococci or to gram-negative bacilli. The rapid progression of infectious processes in young infants frequently necessitates empirical selection of an antimicrobial agent during the first 48 hours of therapy while the causative agent and its sensitivity to various antibiotics are being determined. Since kanamycin is a bactericidal agent effective against the majority of staphylococci, including hospital strains, and most of the gram-negative bacilli, it is an ideal drug for early treatment of newborn infants with fulminating bacterial infections due to unidentified agents. In instances where there is reasonable suspicion that the infection may be due to the less commonly present pneumococcus or beta streptococcus, organisms against which kanamycin is relatively inactive, it may be advisable to use penicillin in addition to kanamycin while bacteriologic studies are being performed. When these studies are complete the appropriate agent may be selected and the other discontinued. This plan of approach is recommended for the management of septicemia of the newborn. Another disease state in which kanamycin is a useful drug is gastroenteritis due to the pathogenic serotypes of *E. coli.* Used orally it provides the same local therapeutic effect in the bowel as neomycin, the drug commonly employed for this disease.

Emergence of bacterial resistance to kanamycin was not a problem in this group of patients. There was good correlation between the in vitro studies of Gourevitch[7] and the in vivo results in patients treated at Jefferson Davis Hospital. There was no evidence that any organism became resistant to kanamycin during an individual course of therapy. Sev-

Table IX. Analysis of deaths of 33 patients treated with kanamycin

Late institution of therapy	11
Overwhelming infection	4
Inadequate dosage to kanamycin	4
Inadequate drainage	4
Death from causes unrelated to infection	10
Total	33

eral kanamycin-treated patients had a recurrence of symptoms and responded satisfactorily to a second course of kanamycin.

The rapid absorption of kanamycin by the intramuscular route is an important factor in its selection for use in seriously ill young children. A drug which may be given intramuscularly is frequently preferable to one which requires either the oral or intravenous route. Oral medication may be contraindicated or difficult to achieve in the critically ill child. Intravenous medication is difficult to administer over an extended number of days. This is particularly a problem in the use of some of the more potent antistaphylococcal antibiotics which cause thrombophlebitis. The latter are limited in their usefulness because of the difficulty of administration and also because they destroy veins necessary for the maintenance of hydration.

The dosage regimen for intramuscular kanamycin currently employed at Jefferson Davis Hospital is as follows: 50 mg. per kilogram per day until there is clinical improvement, 25 mg. until the patient becomes asymptomatic, and 12.5 mg. for a variable period of maintenance depending upon the nature of the infection. In the newborn infant or the child with known impairment of renal function the maximum dose employed is 25 mg. per kilogram per day. The March, 1959, *News-Letter* of the Committee on Control of Infectious Diseases and the Committee on Fetus and Newborn of the American Academy of Pediatrics states that the dosage of kanamycin should not exceed 2 to 4 mg. per kilogram per day for premature and full-term newborn infants.[13] It seems that further clinical studies and blood level determinations are indicated to establish the optimal dosage in this age group.

The severity of toxicity of kanamycin in infants and children is not yet well established. In the 140 patients presented here nephrotoxicity was not a problem. Ototoxicity has not been reported in children receiving kanamycin although it has occurred in adults. Auditory studies of 50 of the children in this series are now in progress. Until the ototoxic potential of this new antibiotic is clarified kanamycin should be reserved for the treatment of serious infections.

SUMMARY

1. Two years of experience with the use of kanamycin sulfate in the management of serious infections in 140 infants and children is reported. The major clinical diagnoses were gastroenteritis, septicemia, pneumonia, pyoderma, subcutaneous abscess, deep abscess, osteomyelitis, omphalitis, thrombophlebitis, and a group of miscellaneous infections. Seventy-eight of the infections were due to *Staphylococcus aureus*, 28 to *Escherichia coli*, 5 to *Klebsiella pneumoniae*, 5 to *Proteus* species, and 1 to β streptococcus. In 23 cases an etiological diagnosis could not be established. The dosage of kanamycin used during the latter part of the study and presently employed is 12.5 to 50 mg. per kilogram per day. The drug was administered intramuscularly and locally. The duration of the therapy depended upon the nature of the infection.

2. Kanamycin was found to be a valuable drug in the treatment of serious infections in infants and children. Its advantages are that it is bactericidal, it is rapidly absorbed following intramuscular injection obviating intravenous therapy, it is active in vitro against the majority of strains of staphylococci, including hospital strains, and against many gram-negative bacilli ordinarily resistant to other antibiotics.

3. The experience gained in this study suggests that the following situations are important indications for the use of kanamycin: initial use in patients with extremely severe infections due to organisms that can be expected to respond to kanamycin; initial use for the treatment of less severe infections due to kanamycin-susceptible bacteria occurring in patients, such as premature infants, in whom a rapid progression of the disease process is anticipated; later use in patients with infections due to organisms found to be resistant to other antibiotics and sensitive to kanamycin.

4. The potential hazards in the use of kanamycin are nephrotoxicity and ototoxicity

as have been reported in adults. There was no evidence that either was a problem in the group of children presented here, although large doses of kanamycin were used and in some instances the drug was administered for long periods. It should be kept in mind that there is increased risk of toxicity in patients who have diminished excretion of the drug due to pre-existing renal disease with decreased glomerular filtration rates.

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Acute constrictive pericarditis

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CONSTRICTIVE pericarditis is an uncommon childhood disease.[1-3] In most instances it begins insidiously, progresses slowly, and extends over a period of years.[3-7] An acute form of the disease occurs, however, which is infrequently documented in the medical literature[8, 9] but is amenable to surgical therapy.[8, 10]

In this report an instance of concretio cordis following acute suppurative pericarditis which progressed to death within 21 days is described. This report emphasizes the relationship between purulent pericarditis and concretio cordis, the rapidity with which the latter may develop, and the necessity for surgical drainage in addition to appropriate antibiotic therapy of purulent pericarditis.

CASE REPORT

A 4-year-old Negro girl was admitted to the Municipal Contagious Disease Hospital in extremis on Sept. 18, 1959. A history of 2 to 3 days of fever, anorexia, vomiting, and lethargy which progressed to coma prompted admission. Petechiae were present on the skin at the initial examination. Lumbar puncture revealed a purulent spinal fluid; many gram-negative diplococci were seen on the smear. The spinal fluid sugar was 5 mg. per cent. Treatment was initiated immediately with tetracycline by intravenous administration. Improvement was prompt. By the fifth hospital day the petechiae had cleared, and the patient was taking oral feedings.

A pericardial friction rub was first noted on the fourth hospital day. Roentgenograms of the chest at that time revealed massive cardiomegaly. The electrocardiogram disclosed alterations of the S-T segment and of the T wave consistent with acute myopericarditis. The friction rub disappeared after one week. No murmurs were heard and the heart tones were not muffled. However, marked hepatomegaly appeared. Daily blood pressure determinations were consistently 80/30 mm. Hg. The pulse varied between 120 and 160 per minute.

Blood and spinal fluid cultured on admission yielded Type II meningococci. Because of persistent elevation of temperature, a second lumbar puncture was performed on the eighth hospital day; the cerebrospinal fluid was entirely normal.

Serial roentgen films of the chest demonstrated a progressive decrease in the size of the heart until there was only moderate cardiomegaly on the seventeenth hospital day. One day previously, facial edema,

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tachycardia, increasing hepatomegaly, and vomiting were noted. A low-grade fever of up to 101° F. persisted. Digitalization was completed during the subsequent 24 hours, with no improvement. Vomiting continued and oliguria developed. At this point, on the twenty-first hospital day, the patient was transferred to Sarah Morris Hospital for Children of the Michael Reese Hospital.

Physical examination on admission revealed pallor, tachypnea, and mild orthopnea. There was generalized edema which involved the face as well as the body. The jugular veins were distended. The pulse was 126 and paradoxical. The blood pressure was 90/70 mm. Hg. The temperature was normal. The precordium was not hyperactive although cardiomegaly could be demonstrated both to the right and to the left of the sternum by percussion. The heart tones were thought to be somewhat muffled. There were no murmurs. The lungs were clear. Marked hepatomegaly was present.

On admission the hemoglobin was 5.8 Gm. per cent. The leukocyte count was 17,000 per cubic millimeter with a marked shift to the left. Urinalysis and serum electrolytes were normal. A roentgenogram of the chest disclosed moderate cardiomegaly. The heart size, in comparison with previous films, however, was markedly decreased. The hilar shadows were engorged. Bilateral minimal pleural effusion and an early right lower lobe pneumonia were present. The electrocardiogram revealed sinus tachycardia, normal voltage, and alterations of the S-T segment and the T wave consistent with subacute myopericarditis. The Mantoux test was negative on two occasions.

Digitalis was continued and a low sodium diet instituted. Two hundred and fifty cubic centimeters of whole blood was administered slowly. There was no improvement at the end of the third hospital day. Despite the addition of chlorothiazide to the therapeutic regimen, there was no change in weight. The patient's temperature increased to 101.4 degrees on the third hospital day. A repeat x-ray of the chest then revealed right middle lobe pneumonia as the only change from the film on admission. Oxygen and antibiotic therapy were started. Pericardiocentesis was considered but not attempted because the marked reduction in cardiac size in serial films led to the conclusion that little pericardial fluid was present. The diagnosis of concretio cordis was rejected because it was felt that too little time had elapsed for the development of such changes. It was inferred, therefore, that the child was suffering from an acute septic myocarditis. She failed to respond to antibiotics, digitalis, and salt restriction. Distention of the veins of the neck and hepatomegaly increased and edema persisted. Lethargy was progressive. The patient died shortly after 8:00 A.M. on the morning of the sixth hospital day, the twenty-first day after the onset of acute pericarditis.

Autopsy report.

Gross. The pertinent gross findings were largely limited to the heart, which, together with the arch of the aorta and fibrous pericardium, weighed 200 grams. The fibrous pericardium was edematous, thickened, and adherent to the lungs and to the thymus, forming a "frozen" mediastinum. The pericardial cavity was completely obliterated by an organizing fibrinopurulent exudate (Fig. 1). The total pericardium measured 8 to 10 mm. in thickness and showed three distinct layers: a middle fibrinopurulent layer (3 mm.) with outer (4 mm.) and inner organizing fibrous layers. The cavity was reconstituted digitally along the fibrinopurulent layer with great difficulty, and the fibrinohemorrhagic exudate in some areas was somewhat yellow in color; in others it was absent, apparently having been organized. The right atrium and right ventricle were greatly dilated. The right ventricle measured 3 mm. in thickness.

There were no significant gross pathologic changes in the lungs. The liver weighed 600 grams; the cut surface showed a dark red parenchyma with exaggerated lobular pattern, nutmeg-like in appearance.

Microscopic. The fibrous pericardium and serous epicardium were replaced by a layer of dense collagenous fibrous tissue.

This was well vascularized and contained focal infiltrates of inflammatory cells consisting principally of lymphocytes and plasma cells (Fig. 2). A zone of progressive organization with prominent endothelial and fibroblastic proliferation at the junction of pericardium and epicardium with the fibrinopurulent layer was noted at this point. Large islands of nuclear debris were also noted in the fibrinopurulent layer. There was a moderate infiltrate of mononuclear cells in the subepicardial connective tissue of both ventricles, but the infiltrate did not involve the adjacent myocardium, and myocarditis was not evident at any point. Marked edema was evident in the connective tissue surrounding the heart and upper mediastinal vessels. Increased vascularity and focal infiltration of lymphocytes were also prominent in these areas.

Sections of the lungs showed focal pulmonary edema, pleural thickening, and finely vascular fibrous pleural adhesions. There was fresh hemorrhage into the pulmonary parenchyma immediately adjacent to some of these adhesions. The picture of the liver was that of a very severe passive hyperemia with focal centrilobular necrosis. Permission for examination of the head was not granted.

DISCUSSION

The etiology of constrictive pericarditis is obscure.[1-7] In most patients no definite etiological agent can be established even after examination of both surgical and autopsy material. A significant proportion of cases follow tuberculosis, which is the etiological factor in as many as 80 per cent of cases in some series.[8-10] Constrictive pericarditis may, however, also follow acute benign pericarditis,[11] hemopericardium,[12] and radiation pericarditis.[8] Acute rheumatic fever, although it commonly produces acute pericarditis, does not produce constrictive pericarditis.[9] Acute suppurative pericarditis leading to constrictive pericarditis is a rare sequence of events and some have doubted its occurrence.[2] Andrews and associates[9] in a review of the literature up to 1948 and among their 7 cases could find no case of

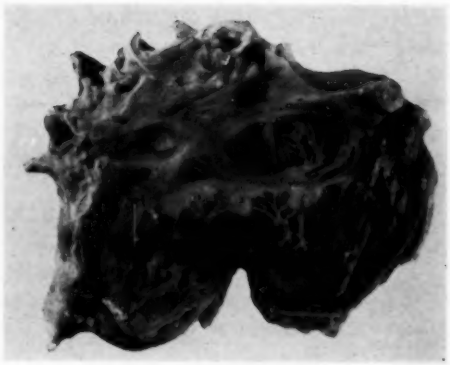

Fig. 1. Gross view of the heart at autopsy with the right ventricle and right atrium opened. The thick pericardium encasing the myocardium is shown.

constrictive pericarditis which occurred in the healing phase following acute suppurative pericarditis. Shipley and Winslow[16] in 1935 reported upon 39 patients who survived an attack of acute purulent pericarditis and who were subsequently followed for 1 to 32 years. None of these was conclusively shown to have developed constrictive pericarditis. Two patients had residual cardiac disability and were said to have "adhesive" pericarditis. These patients may have had concretio cordis.

In contrast to other authors,[13-15] Blalock and Burwell[10] reported 3 cases of constrictive pericarditis following purulent pericarditis; 2 of these patients underwent successful pericardectomy. Gimlette[8] reported a fatal case secondary to a subphrenic abscess caused by *Escherichia coli*. More recently, acute purulent pericarditis due to tularemia has been shown to produce constrictive pericarditis.[17, 18]

Acute suppurative pericarditis is rare; most large series were observed and reported in the pre-antibiotic era.[16, 19, 20] Since the preceding process, acute suppurative pericarditis, is, in itself, rare, the occurrence of concretio cordis complicating acute suppurative pericarditis must be extremely rare. Deterling and Humphreys[15] reported an incidence of 15 per cent for acute suppurative pericarditis in a series of 416 cases of acute

pericarditis. Keith, Rowe, and Vlad[1] reported an incidence of 25 per cent of the cases of acute pericarditis at the Hospital for Sick Children where acute pericarditis was present in one out of every 1,250 admissions. Moreover, acute purulent pericarditis was often a fatal disease, the mortality rate in larger series varying from 80 to 100 per cent.[1, 19]

The organisms most commonly involved are the staphylococcus, streptococcus, and pneumococcus; the meningococcus is a rare etiological agent. Herrick[19] reported a large series of cases of meningococcal meningitis in 5 per cent of which acute purulent pericarditis was a complication. Others have reported similar, though isolated cases. *Hemophilus influenzae, E. coli, Pseudomonas aeruginosa, and Bacterium tularense* have also been implicated on rare occasions. Most cases occur as a complication of other severe septic processes such as pneumonia, empyema, osteomyelitis, wound infections, and bacterial meningitis.

It appears, therefore, that an insufficient number of survivors remained to demonstrate that acute purulent pericarditis can progress to constrictive pericarditis. With the use of potent antibacterial agents the incidence of constrictive pericarditis may be altered. Levine[12] suggests that recovery from the acute process will occur in many more cases of acute suppurative pericarditis but some of these will become chronic and progress to constrictive pericarditis in future years. By sterilizing the purulent exudate in the pericardial space, antibiotic therapy can prevent death from sepsis during the acute phase. As with purulent exudate in any localized space, however, the exudate organizes rapidly with the development of a dense fibrotic scar, unless it is drained.

Our case not only illustrates a clear relationship between purulent pericarditis and constrictive pericarditis but indicates that constrictive pericarditis can be a rapidly developing disease. Similar experience has been reported following acute benign pericarditis,[11] tularemic pericarditis,[17] and tuberculous pericarditis.[9] In these cases concretio cordis developed in 2 to 3 months to 2 years after the acute episode. Andrews and coworkers[9] reported an interesting series of 16 cases of acute tuberculous pericarditis associated with pericardial effusion, enlarged cardiac roentgen shadows, and congestive heart failure. Signs and symptoms of congestive failure persisted into the stage of chronic constrictive pericarditis despite a decrease in size of the heart almost to normal.

Although concretio cordis occasionally develops rapidly during the course of tuberculous pericarditis, the remarkable speed with which constriction developed in our case is not seen in tuberculosis. The difference, doubtless, is due to the extent of the acute inflammatory changes induced by suppurative organisms as compared to those produced by the tubercle bacillus.

When signs of congestive cardiac failure develop, accompanied by a rapidly enlarging cardiac silhouette and relatively hypovascular lung fields and elevation of the S-T segment in the electrocardiogram during the course of an acute septic process, acute suppurative pericarditis must be suspected. Unresponsiveness to digitalis and the presence of a friction rub substantiate the diagnosis. Under such circumstances a diagnostic pericardiocentesis is indicated. This should not be omitted because of the apparently favorable resolution of the toxic manifestations by vigorous antibiotic therapy. If purulent exudate is demonstrated in the pericardial space, open drainage is indicated. Pericardiocentesis is a useful diagnostic procedure but is usually inadequate for effective drainage.[3] Open pericardiectomy alone, without antibiotics, has been shown to have reduced the mortality of suppurative pericarditis considerably.[16]

Constrictive pericarditis must be considered as a possible complication if signs of congestive heart failure persist despite adequate therapy following acute purulent pericarditis. The cardiac silhouette often decreases dramatically after antibiotic therapy and the lung fields remain relatively free of congestive changes, but generalized edema,

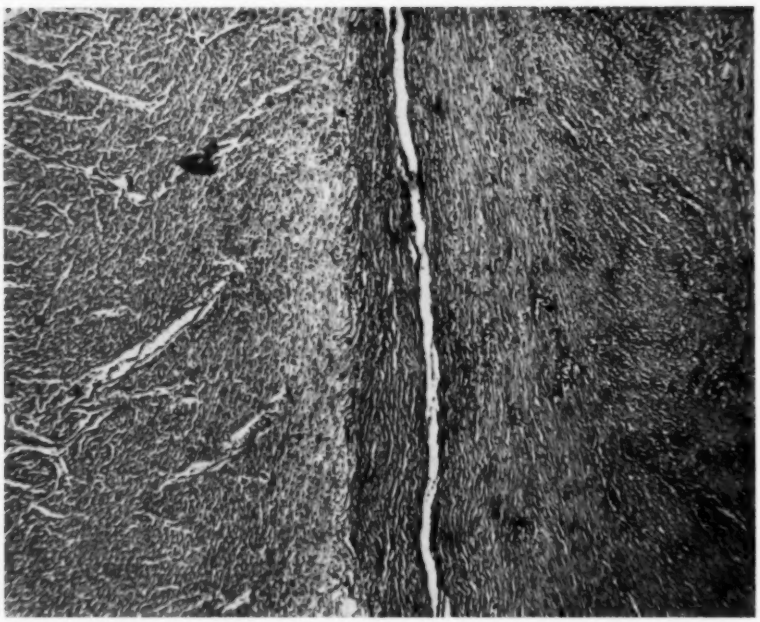

Fig. 2. Microscopic section through the myocardium and pericardium. The myocardium is seen to the right and the thickened fibrous pericardium is evident on the left. (Original magnification ×30.)

markedly elevated venous pressure, gross hepatomegaly with ascites, and signs of reduced cardiac output, all unresponsive to the continued administration of antibiotics and digitalis, suggest the development of constrictive pericarditis. A quiet precordium, distant heart tones, narrowed pulse pressure, pulsus paradoxus, and a loud early diastolic shock, when present, are helpful additional diagnostic signs. A similar clinical picture can be produced by toxic myocarditis.[21] Often these two factors are additive in their effects on cardiac function.

Constrictive pericarditis is rarely an isolated factor in the production of myocardial insufficiency, and variable degrees of muscle inflammation, injury, and atrophy usually are present.[8, 21] Although pericardiectomy is a well-established surgical procedure with successful outcome in 40 to 80 per cent of cases,[3, 10] in some the signs and symptoms of congestive heart failure persist and require maintenance digitalis therapy despite apparently adequate surgical procedures. Better operative results and less residual cardiomegaly are seen in those cases of shorter duration, and presumably with lesser degrees of myocardial injury. Data obtained at cardiac catheterization cannot always differentiate between the degree of myocardial embarrassment produced by mechanical constriction and that produced by intrinsic myocardial disease, since each produces similar hemodynamic alterations. If constrictive pericarditis is suspected, pericardiectomy is indicated, in the knowledge that the results of therapy depend upon the functional integrity of the underlying myocardium.

SUMMARY

A case of acute constrictive pericarditis secondary to meningococcal infection is presented. Fatal concretio cordis developed with unprecedented speed 21 days after the onset of suppurative pericarditis. The literature is reviewed pertaining to the relationship of suppurative pericarditis and subsequent concretio cordis. It is emphasized (1) that con-

strictive pericarditis may develop acutely, and (2) that antibiotics alone afford inadequate treatment of suppurative pericarditis, but must be combined with surgical drainage.

We are indebted to Dr. R. Cullen of the Department of Pathology for performing the autopsy examination.

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Successful treatment of Histoplasma meningitis with amphotericin B

A case report

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ONE is impressed by the paucity of clinical reports of involvement of the central nervous system after infection with *Histoplasma capsulatum*. In a review of the literature we were unable to find any such cases diagnosed before death. This is surprising in view of several reports of necropsies indicating that involvement of the central nervous system is common. Shapiro and colleagues[1] reported involvement of the central nervous system in 6 of 11 cases with disseminated histoplasmosis in which the brain was examined. Schulz[2] reviewed 120 necropsies of cases of histoplasmosis, in 12 or 10 per cent of which cerebral or meningeal involvement, or both, were noted. Rubin and associates[3] reported cerebral involvement in 5 of 17 necropsies, an incidence of 29 per cent. Duarte[4] predicted that, if the brain were examined in all cases, an even higher incidence of involvement of the central nervous system would be found.

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Although there have been an increasing number of reports[5-9] of successful treatment of disseminated histoplasmosis with amphotericin B, in none of these patients has involvement of the central nervous system been identified. The following case is believed to be the first recorded instance of successful treatment of meningitis due to *Histoplasma capsulatum*.

CASE REPORT

A 5-year-old white boy, a resident of northern Louisiana, was admitted to Ochsner Foundation Hospital on Jan. 26, 1958, because of intermittent fever since the age of 15 months. He was observed in the hospital for a period of 9 days, during which time his temperature fluctuated widely, rising repeatedly to 103° or 104° F. Although he was obviously a very sick boy, no specific abnormalities could be found on repeated physical examination or in the results of the many laboratory tests. These included the skin test for histoplasmosis, which was negative. He was discharged without a diagnosis and instructed to take tetracycline, 0.5 Gm. daily, and to return in one month.

On the second admission, 3 weeks later,

he was still febrile, and at this time the liver and spleen were enlarged. Liver biopsy was performed. Grossly, the liver was studded with tiny miliary granules, which, on microscopic examination, were seen to contain *H. capsulatum*. Ironically, one day following this operation, the blood culture taken a month before was reported to show abundant growth of the same organism.

Treatment with triple sulfonamides in high dosage by mouth was immediately instituted in order to maintain a blood sulfonamide level of about 15 mg. per cent. However, the boy's condition deteriorated rapidly. The liver and spleen enlarged to 12 cm. below the costal margins, extensive pneumonitis with cyanosis and dyspnea appeared, purpura became evident, and hemograms indicated progressive depression of all cellular elements including platelets. For a time the child seemed moribund and required vigorous supportive therapy.

About this time it was first noticed that there was weakness of the right lower extremity with ankle clonus and a Babinski reflex on this side. A positive Kernig sign was elicited, and funduscopic examination revealed what appeared to be two retinal granulomas, one in each eye. Spinal puncture was therefore performed on April 19, 1958; the cerebrospinal fluid contained 68 white blood cells per cubic millimeter (53 lymphocytes and 15 neutrophils). The protein level was 12 mg. per 100 ml.; the sugar, 50 mg. per 100 ml. Cultures of this fluid were sterile on media designed for Histoplasma (Littman agar, Sabouraud-dextrose, and trypticase soy agar with 5 per cent rabbit blood), both at room temperature and at 37° C.

With continued treatment the child gradually improved. The lungs cleared, hepatosplenomegaly disappeared, and the blood count returned to normal. After 6 weeks he became afebrile and was released from the hospital to continue taking sulfonamides at home.

This period of outpatient observation lasted a year—from September, 1958, to September, 1959—during which time the child continued to take sulfonamides for a total of 9 months' therapy, and returned at regular intervals for blood counts, determinations of sulfonamide levels, and spinal taps. As will be seen in Table I, there was no significant clearing of the meningitis. Although the child remained active and felt relatively well, he still suffered recurrent headaches and had occasional brief but mild episodes of fever. The spinal fluid continued to show pleocytosis with increased protein and diminished sugar levels. On April 23, 1959, a pneumoencephalogram was made. All ventricles and subarachnoid sulci filled well and were of normal appearance. There was no sign of cerebral atrophy.

Because of the apparent failure of sulfonamides to clear the meningitis, it was decided in September, 1959, to begin treatment with amphotericin B. The child was admitted to the hospital, where a polyethylene catheter was placed in a large brachial vein to provide access for daily intravenous infusions. Each day except Sunday the child received an infusion of 250 ml. of 5 per cent glucose solution containing the calculated dose of amphotericin B, administered slowly over a 4 to 6 hour period. After the infusion the catheter was flushed with heparin and then capped so that the child could resume ambulatory life in the hospital until time for his next infusion. The first dose of amphotericin B was 0.25 mg. per kilogram of body weight. The dose was gradually increased until after a week he was receiving the full daily dose of 1 mg. per kilogram of body weight. During a period of 75 days, the patient received sixty such full doses. As will be seen in Table I, response to this treatment was immediately favorable and, before the end of the course, the spinal fluid was normal except for a persistently elevated protein level.

Some untoward effects from amphotericin were observed. Nausea and vomiting were troublesome at times, but for the most part could be averted by slow infusion, premedication with chlorpromazine, and later by addition of pyridoxine to the infused fluid. Azotemia was expected, and, as Table I

Table I. Results of spinal fluid studies and blood urea nitrogen levels in patient with *Histoplasma capsulatum* meningitis

Date	*CSF cell count (per mm.³)*	*Lympho-cytes*	*Neutrophils*	*Protein (mg. %)*	*Glucose (mg. %)*	*Chloride (mEq./L.)*	*Blood urea nitrogen (mg. %)*
4/1/58	68	53	15	12	50	119	12
4/28/58	2	2	0	16	51	117	
9/5/58	304	304	0	65	44		11
9/10/58	240	—	—				
9/19/58	74	72	2	72			
10/6/58	111	110	1	62	42		
11/14/58	67	62	5	62	33	120	9
1/3/59	54	52	2	44	39	124	
3/13/59	93	91	2	109	36	119	
4/21/59	115	109	6	158	33	118	
4/23/59	227	220	7	149	33		
6/23/59	62	62	0	81	22	121	
7/26/59	75	73	2	60	29	120	
8/31/59	49	48	1	95	38		7
9/1/59	Amphotericin B therapy begun						
9/1/59							37
9/15/59	45	43	2	51	66		47
	Intrathecal Amphotericin B given 9/15/59 and 9/18/59						
9/18/59	21	21	0	46	56		42
9/28/59	9	9	0	151	73		44
10/5/59	10	10	0	150	75	133	54
10/15/59	14	14	0	149	75	130	62
10/27/59	2	2	0	118	78	131	45
11/14/59	Amphotericin B therapy completed						
11/16/59	0	0	0	70	64	130	74
11/18/59							62
12/9/59	3	2	1	49	64	129	17
2/4/60	2	2	0	32	61		16
5/16/60	1	1	0	22	70	121	16
8/12/60	1	1	0	22	81	122	11

shows, appeared promptly and reached alarming heights. Since permanent renal damage from this drug has never, to our knowledge, been reported, treatment was continued despite the high blood urea levels. The urine remained normal throughout, and after completion of therapy the uremia promptly disappeared.

On Sept. 15, 1959, we injected 0.5 mg. of amphotericin B, mixed with 1 ml. of cerebrospinal fluid, into .the spinal canal. This caused temporary numbness and paresthesia of one leg. Three days later a similar dose was given, this time mixed with 20 mg. of hydrocortisone, and followed by 2 c.c. of air, after which the patient was rocked to disseminate the drug. Within a few hours the child had complete paralysis of the right third and seventh cranial nerves, and both legs were entirely flaccid. Cranial nerve function returned in a day, but function of the legs improved much more slowly, and now, 11 months since the injection, although the child walks, he does so with a steppage gait, and on examination presents bilateral foot drop with weak peroneal muscles. Tendon reflexes are absent in the left leg, and present but diminished in the right leg, where the Babinski sign, noted before treatment, still persists.

All treatment was terminated Nov. 14, 1959, the child having completed the arbitrarily planned course of sixty full doses. Since then, frequent examinations of spinal fluid, blood counts, and tests of sedimentation rate have been made. These are partially recorded in Table I, and have shown no evidence of recurrence of the meningitis. Clinically, the child remains well except for his abnormal gait. Now, 10 months after

completion of therapy, he is happy at home, living an active life. He enjoys fishing and water skiing, attends school regularly, has passed the first grade, and looks forward to beginning second grade in the fall.

Finally, it is interesting that the reaction to the skin test for histoplasmosis, which was negative while the child was sick, became positive during convalescence, and that his mother and sister both had positive cutaneous reactions to histoplasmin. The whole family has had close contact with chickens during frequent weekend visits to a farm.

COMMENT

Chronic meningeal infection was a complication of disseminated histoplasmosis which was not suspected during the initial study of this patient. Spinal puncture, in fact, was not performed until after therapy with sulfonamides had rescued the child from a moribund condition, when early signs of spastic monoplegia were first noticed. In retrospect, it seems possible that meningeal involvement might have been present from the beginning, and it would seem wise in the future to study all cases of systemic histoplasmosis for evidence of meningeal involvement.

The clinical picture of Histoplasma meningitis, judging from this case and 3 cases seen by Christie,[10] seems to be similar to that of tuberculous meningitis. Lymphocytic pleocytosis in the cerebrospinal fluid is noted, with elevation of protein and depression of sugar levels, and the disease runs a chronic and usually fatal course. None of Christie's patients survived. From a review of the literature it would appear that our patient represents the first recorded recovery from meningitis due to *H. capsulatum*.

Confirmation of the diagnosis by demonstration of *H. capsulatum* in the cerebrospinal fluid was not accomplished in the present case, possibly because of the vigorous use of sulfonamides before the initial spinal puncture. Nevertheless, in view of the positive cultures from the blood, there seems to be no reasonable doubt that the meningitis was indeed caused by this organism.

Regarding the proper treatment of disseminated histoplasmosis, there is still no unanimity of opinion. Amphotericin B is often effective, but is toxic. For this reason, Christie[11] has favored the use of sulfonamides. In his experience sulfonamides have shown an ability to retard the growth of *H. capsulatum*, allowing time for the body's defenses to take over and eventually eradicate the infection. He reported recovery in 5 patients with disseminated histoplasmosis treated with sulfonamides.

Our patient was therefore given vigorous and prolonged therapy with sulfonamides, the blood sulfonamide level being maintained between 12 and 18 mg. per 100 ml. for 9 months. The response in general was gratifying. Indeed, it appeared that all manifestations of histoplasmosis were overcome by this therapy with the single exception of the meningeal component. At long last we resorted to amphotericin treatment and were rewarded by prompt, rapid clearing of the abnormalities in the cerebrospinal fluid. In retrospect, we believe that amphotericin should have been given earlier; the sulfonamides controlled the systemic infection nicely, but were ineffective against the meningitis.

The toxicity of amphotericin B has been well described by Seabury,[5] and is illustrated by the case herein reported. Nausea and vomiting were not hard to control, but progressive azotemia caused grave concern. Some observers favored discontinuance of therapy when the blood urea nitrogen level reached 62 mg. per cent. However, in the past this effect of the drug has always been reversible, so we persisted with treatment despite the rising blood urea levels, and in the end no harm was done. At no time did the urine contain albumin, casts, or red blood cells, nor did hypertension or other sign of renal disease appear. After discontinuance of treatment, the blood urea nitrogen level quickly returned to normal (Table I).

Intrathecal therapy was attempted because Seabury[5] observed that the drug given intravenously does not enter the cerebrospinal fluid unless the protein level of the spinal fluid is high. He used this route routinely in

treating cryptococcal meningitis, without any untoward reactions more serious than transient root pains and paresthesias. In our patient, by contrast, intrathecal administration, performed with great caution and in strict accordance with Seabury's technique, produced disastrous results. After the injection the boy became totally paralyzed in both legs and, although he has greatly improved, he still has bilateral foot drop, which is likely to be permanent. Henceforth, we shall be extremely reluctant to give amphotericin by the intrathecal route.

SUMMARY

A case of meningeal histoplasmosis in a young boy was successfully treated with amphotericin B, after failure of sulfonamide therapy. The toxic effects of intravenous therapy with amphotericin were alarming but transitory. Intrathecal administration, however, caused paralysis of both legs, which was only partially reversible. We recommend spinal fluid studies in all cases of disseminated histoplasmosis, and prolonged intravenous administration of amphotericin in patients who have meningeal involvement. This case appears to be the first recorded cure of meningitis due to *Histoplasma capsulatum*.

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Intracardiac myxoma involving the right and left atria in a young patient

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ATRIAL myxomas are rare in patients in the pediatric age group. We found only 9 such reports out of some 200 enumerated cases in the available literature.

Because surgical cure is now possible, the clinical recognition of the varying syndromes that may be produced by such tumors is of obvious importance. The present study concerns a myxoma diagnosed at autopsy in an 11-year-old boy. This case is unusual in that the tumor involved both sides of the heart and produced symptoms of emboli to both pulmonary and systemic systems. The clinical manifestations of atrial myxomas are reviewed, with emphasis on those occurring in the pediatric age group.

CASE REPORT

First admission. An 11-year-old boy was first admitted to the hospital in July, 1958, following an episode of syncope. Two months previously he was awakened with painful pale feet described by his mother as looking "frost bitten." These symptoms cleared in an hour with local application of heat, but recurred periodically, sometimes accompanied by a transient macular rash on the lower legs. In addition, for the previous year he had complained occasionally of morning headaches. On the day of admission, while playing outside, he suddenly collapsed and momentarily lost consciousness. He was carried to his home where paralysis of the right arm and leg and difficulty with speech were noted. On admission to the hospital the only abnormal signs were neurological, with increased tendon reflexes, muscle weakness, a positive Babinski reflex on the right side, right facial paresis, and aphasia. The symptoms and signs disappeared overnight. Laboratory investigation revealed a hemoglobin of 11.1 Gm., a sedimentation rate of 45 mm. per hour, a normal white blood count and differential and a normal urinalysis. Skull x-ray was normal; an electroencephalogram suggested diminished activity on the right side, a left carotid angiogram was normal. A chest x-ray showed a heart shadow a little wider than usual, but clinical examination of the cardiovascular system was unremarkable.

After discharge he continued to feel well except for occasional morning headache and paresthesia of the left hand. Three months

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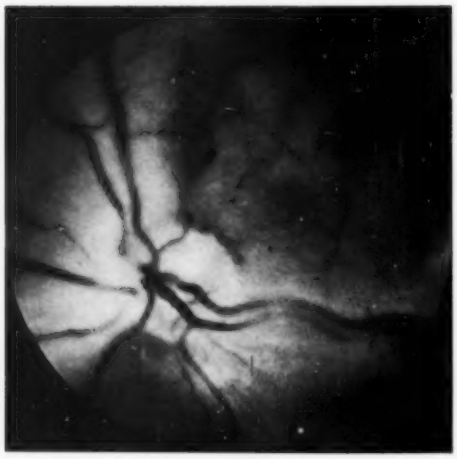


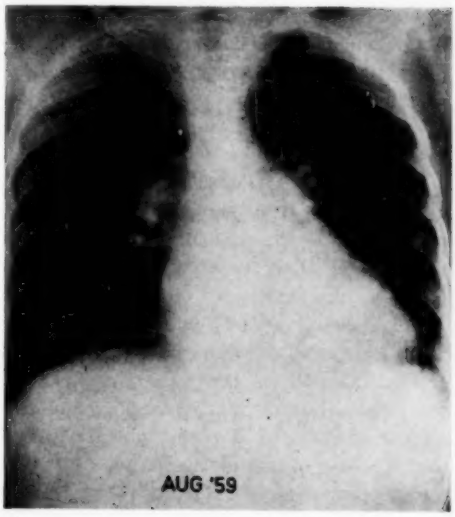
Fig. 1. Fundus showing retinal edema, nasal pallor, and arteriolar narrowing.

later he was seen because of a pleuritic pain in the right side of the chest and a low-grade fever lasting one week. Physical examination was negative and chest x-ray was unchanged. Five further episodes of pleuritic pain and mild fever were subsequently noted.

Second admission (January, 1959). While playing outside, he became dizzy and sat down. He then lost consciousness for 3 minutes and awoke complaining of weakness in the right arm, "pins and needles" in the right hand and both feet, and a frontal headache. These symptoms cleared in a few hours. Physical examination showed slight paresis of the right arm, but normal tendon reflexes. Heart examination was normal. Femoral pulses were recorded as absent. He returned to school after one week in the hospital.

Final admission (August, 1959). While watching television his head suddenly turned to the left, he cried out, and started convulsing, more on the left than the right. On admission to the hospital he was vomiting, incontinent, irritable, not responding to questions, and again demonstrated a right hemiparesis. He remained comatose for 3 days, and the hemiplegia persisted. Examination of the cardiovascular system now revealed definite abnormalities. Blood pressure was 100/65; pulse 90, regular. The apex beat was thrusting and suggestive of left ventricular hypertrophy. The mitral first sound was loud, as was the pulmonary second sound. There was an abnormally loud third heart sound but no opening snap. There was a blowing Grade 3 apical systolic murmur and a faint diastolic murmur at the apex. The murmurs did not change with variations in posture. The femoral and popliteal pulses were normal, but the dorsalis pedis and posterior tibial pulses were diminished, particularly on the right side. There were no carotid or cranial bruits, and the carotid artery pulses were normal. The fundi (Fig. 1) showed arteriolar narrowing, edema, and striking pallor of the nasal half. The chest x-ray (Fig. 2) showed moderate cardiac enlargement and considerable pulmonary congestion. The electrocardiogram (Fig. 3) illustrated notched "P" waves and changes consistent with left ventricular hypertrophy. The hemoglobin was 9.8 Gm., sedimentation rate 36 to 58 mm. per hour, urinalysis negative, serum iron 39 mg. per cent, cholesterol 275 mg. per cent, 3 blood cultures negative, antistreptolysin titer 240 units, C-reactive protein 2-plus, serum glutamic pyruvic transaminase 100 units, serum glutamic oxalacetic transaminase 62 units, and spinal fluid and serum electrolytes normal. Total plasma protein was 6.2 Gm. and the electrophoretic pattern was normal except for a slight elevation of the alpha 2 globulin.

The provisional diagnosis was myocarditis, possibly rheumatic with embolic phenomena, and a ball valve type of left atrial thrombus was suspected. He was treated with digitalis, steroids, anticoagulants, and penicillin. Gradual improvement ensued. After one week he was able to sit up in bed and feed himself, but the aphasia and hemiparesis remained. The apical systolic murmur decreased as did the radiologic evidence of pulmonary congestion. Five days later he had another grand-mal seizure, followed by cardiac arrest. Heart massage and intubation were successful but death occurred 20 hours later without restoration of consciousness.



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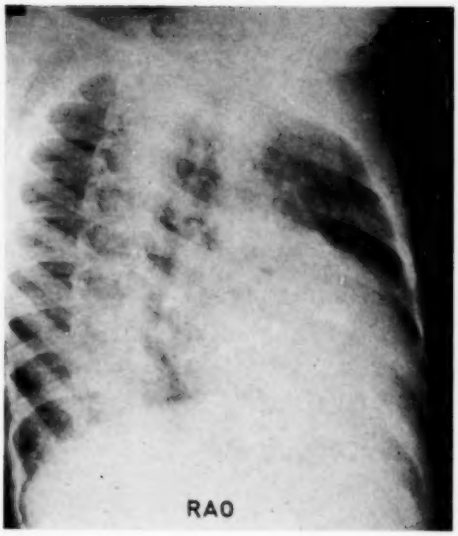

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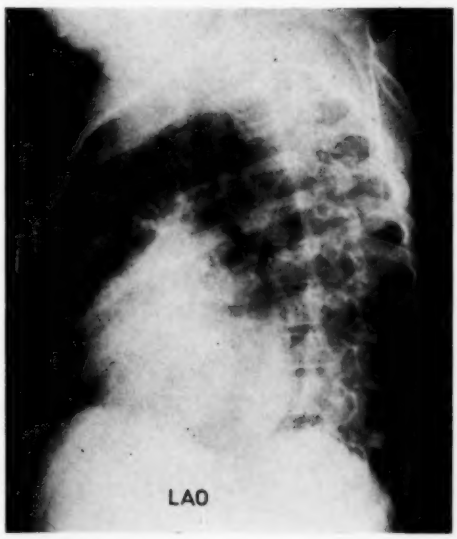

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Fig. 2. Chest x-rays. *A*, Posteroanterior view, generalized enlargement. *B*, Showing left atrial enlargement. *C*, Showing left ventricular enlargement.

Autopsy. The heart weighed 500 grams, with dilation of the left atrium and ventricle. A large myxoma (9.0 by 4.2 by 3.0 cm.) arose by a pedicle from the left side of the atrial septum near the foramen ovale, filled the entire left atrium, extended through the mitral valve to fill part of the left ventricle, and also extended through the foramen ovale to form a mass 3.5 by 2.0 by 1.0 cm. in the right atrium (Fig. 4). The histologic appearance was typical of a myxoma.

The left internal carotid and middle cerebral arteries were filled completely with myxomatous tissue. The left cerebral hemisphere showed areas of infarction. Several medium and small-sized arteries in the lungs showed tumor emboli (Fig. 5). The splenic and right renal arteries contained tumor and these organs showed evidence of old infarction. There was a saddle embolus at the aortic bifurcation occluding both iliac arteries. The latter may have been a terminal event.

DISCUSSION

Considering the size of the tumor the complete lack of cardiac symptoms was surprising. Apart from the embolic phenomena there was almost perfect mimicry of active rheumatic heart disease during the final illness. The patient had red hair, frequent epistaxis, episodic fever, a mild anemia, a consistently elevated sedimentation rate, and an antistreptolysin titer of borderline level. The cardiac findings were

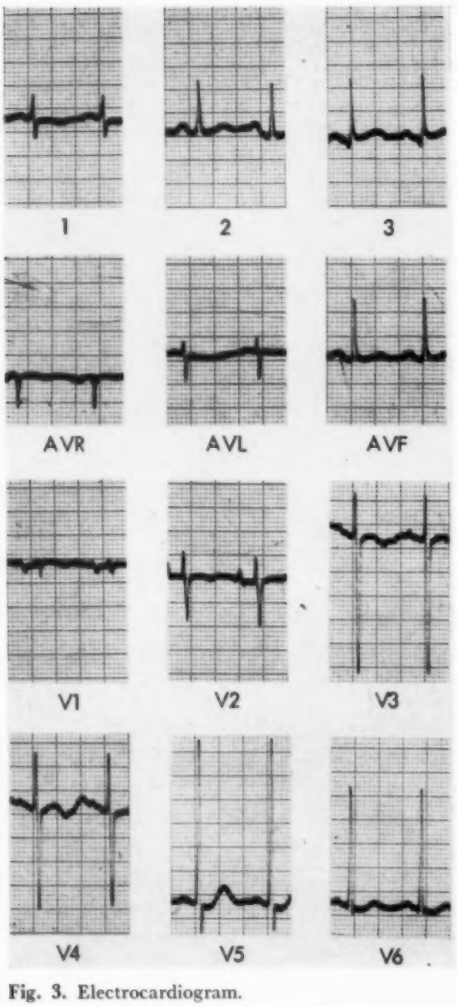

Fig. 3. Electrocardiogram.

typical of active rheumatic mitral disease occurring in the child, with signs of mitral insufficiency and left ventricular failure. Finally the systolic murmur decreased and the congestive failure improved on therapy for rheumatic carditis. The embolic phenomena were explained on the basis of mural thrombi or a ball thrombus in the left atrium, and an angiocardiogram was to have been performed as soon as the patient's condition improved sufficiently.

The recurrent chest pains of pleuritic type are thought to have been due to pulmonary emboli originating from the right atrial component of the tumor. Such symptoms have not been reported in right atrial myxomas.

Pathologic proof of pulmonary emboli was obtained in the present case.

It is usually stressed that the clinical picture of left atrial myxoma mimics mitral stenosis,[2, 3] not mitral regurgitation as in this patient. Left ventricular hypertrophy on clinical, radiologic, and electrocardiographic examinations is most unusual in left atrial myxomas and discouraged the correct clinical diagnosis in the present case. However, emboli are distinctly rare in rheumatic disease in children. Embolic phenomena in the absence of atrial fibrillation are uncommon at any age and it has been recently stressed by Campeau and David[4] that this is an important clue in the diagnosis of atrial myxoma.

The unusual funduscopic changes observed in this patient can be explained by severe vasospasm. Emboli of one central retinal artery has been reported in myxoma[5, 6] but the changes here were bilateral, not only on the side of the carotid occlusion.

A summary of reported atrial myxomas in pediatric patients is shown in Table I. Although over 200 cases of atrial myxoma have been recorded in the literature, only 9 have occurred in children under 16 years of age. Two myxomas were in the right and 7 in the left atrium, and the present case involved both atria.

Despite the low incidence of myxomas in children, the first case diagnosed during life was that described by Goldberg and colleagues.[7] The diagnosis was made by angiocardiography in a 3-year-old girl who had had 2 episodes of cerebral emboli and hemiplegia. Of 5 well-documented reported cases of left atrial myxoma in children, 4 had cerebral emboli. This would seem to be an important diagnostic clue, especially in children, as other causes of cerebral emboli are rare. Four of 5 of the undiagnosed cases were all considered to have rheumatic heart disease, and bacterial endocarditis was strongly suspected in 2 of them. In contrast

to the present case all these children had cardiac symptoms.

Myxomas arising in cardiac sites other than the atria have also been reported in pediatric patients. Reddy and associates[8] found a myxoma on the aortic valve in a stillborn infant; another has been found on the pulmonary valve[9]; and a third at the auriculoventricular node producing a heart block.[10]

To gain a better indication of the findings in left atrial myxoma, 30 well-documented recently described cases (unselected as to age) have been reviewed.

The incidence of major symptoms as listed in the case reports are outlined in Table II. Only one patient failed to have any cardiac symptoms. Of note is the high incidence of emboli (over half of the cases), and in all but one of these patients the emboli lodged in cerebral vessels. While postural symptoms are suggestive of the diagnosis, they were present in less than a fifth of the cases. Patients may present with fever and splinter hemorrhages and closely simulate the syndrome of bacterial endocarditis.

The auscultatory findings in left atrial myxoma are listed in Table III. There may be no abnormalities. Most frequently the sounds mimic those of mitral stenosis, with a loud apical first and pulmonary second heart sounds, mid-diastolic and presystolic murmurs, and occasionally an opening snap. Almost as frequently however, a systolic murmur indicating mitral insufficiency is heard, and, in several instances this was the predominant murmur. Thus, to say that the clinical picture of left atrial myxomas always simulates pure mitral stenosis may be quite misleading. Despite the systolic murmur the remainder of the clinical findings, electrocardiogram, and x-rays are usually more in keeping with mitral stenosis, rather than regurgitation.

The incidence of electrocardiographic changes is shown in Table IV. The majority of cases showed definite abnormalities, the most frequent being right ventricular hypertrophy. Definite P mitrale waves may occur. No case showed left ventricular hypertrophy

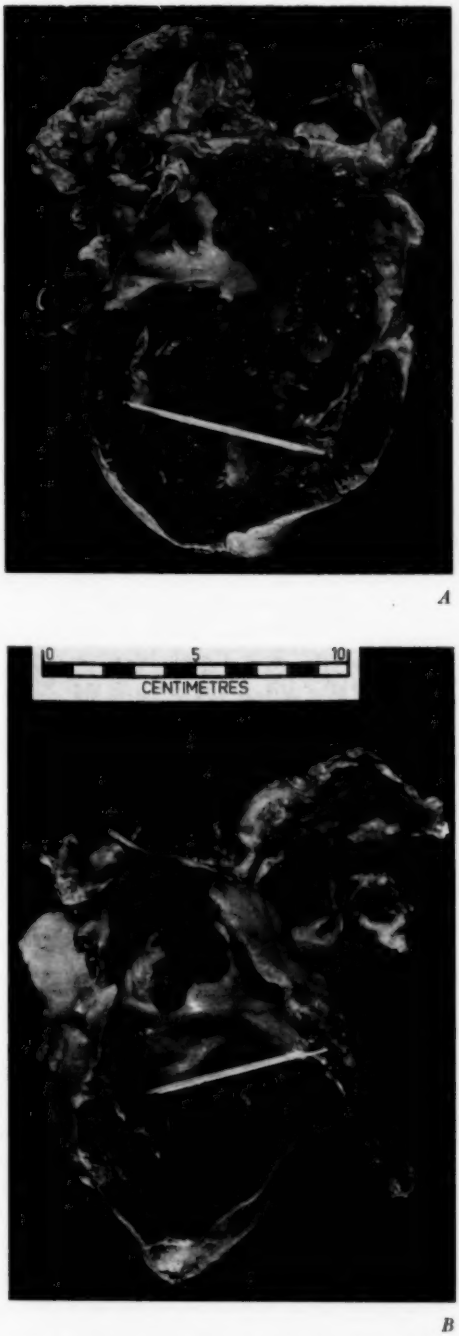

Fig. 4. Gross specimen. *A*, Left atrial and left ventricular portion of tumor. *B*, Right atrial portion of tumor.

Table I. Atrial myxoma in infants and children

Case	Reference	Age	Sex	Clinical diagnosis	Site	Symptoms	Murmurs	X-ray	ECG	Course
1	15	4	F	—	Left atrium appendix			Details not available		
2	15	5	M	—	Left atrium appendix			Details not available		
3	7	3	M	Myxoma	Left atrium	Presented with cerebral emboli	Apical systolic, variable presystolic	Left atrium + Right ventricle +	Normal	Diagnosis by angiography; death at operation
4	13	3½	F	Rheumatic fever	Left atrium	Anorexia, fatigue, leg pain, cough, dyspnea	Systolic with gallop	General enlargement	Right ventricular hypertrophy, P mitrale wave	Progressive heart failure
5	19	8	F	Myxoma	Left atrium	Cerebral and femoral emboli	None	Normal	Normal	Myxoma at embolectomy; angiography; operation under hypothermia
6	16	9	F	Rheumatic fever, subacute bacterial endocarditis	Left atrium	Dyspnea, orthopnea	Apical systolic, diastolic	Left atrium + General	P mitrale wave	Cerebral emboli with convulsion and death
7	Authors'	11	M	Rheumatic fever	Left atrium and right atrium	No cardiac symptoms, 3 emboli to left carotid artery, periodic chest pain	Loud apical systolic, apical diastolic, gallop	Left atrium + Right ventricle +	Left ventricular hypertrophy, bigeminy	Episodes of hemiplegia
8	19	13	F	Rheumatic fever, subacute bacterial endocarditis	Left atrium	Syncope, cerebral embolus	Diastolic gallop	General	Fibrillation	Embolus, sudden death
9	17	14	M	Myxoma	Right atrium	Precordial pain at age 6, dyspnea at age 12, palpitations	Systolic murmur, lower right sternal border	Right ventricle +, calcified mass	Right ventricular hypertrophy, right bundle branch block	Confirmation by angiocardiography; successful operation
10	18	16	M	Myxoma	Right atrium	Fatigue, dyspnea 4 years' duration	Systolic at lower sternal edge	Right atrium + Right ventricle +	A-V block, incomplete right bundle branch block	Death at operation

as was present in our case. Rhythm changes (atrial fibrillation and bigeminy) occasionally occur. Bigeminy occurred in our case during digitalization, with a dose of digitalis not usually associated with toxicity.

Pulmonary artery pressures were available in 12 of the cases reviewed. Severe pulmonary hypertension with systolic pressures over 70 mm. Hg was present in 9 and moderate elevations in the remaining 3 cases. One case[11] showed a fluctuation of pulmonary artery and wedge pressures suggesting intermittent obstruction to flow, which may have originated at the mitral valve or at the orifices of the pulmonary veins. The left atrial pressure curve in one case[12] measured at operation was of the plateau type seen in mitral regurgitation, as was that of the wedge pressure in one case.

The laboratory findings in left atrial myxoma have not been previously stressed. About half the cases reviewed showed sedimentation rates in excess of 20 mm. per hour, and hence confusion with rheumatic "activity." In a quarter of the cases where data were available, the hemoglobin level was under 11.0 Gm. per cent and a quarter of the cases also showed white blood counts of 10 to 20 thousand cubic millimeter. The chest x-ray is usually abnormal in myxoma, the majority of cases showing some left atrial enlargement (usually not marked). There may be general enlargement with the right ventricle primarily involved, and dilated pulmonary arteries and pulmonary vascular congestion.

The clinical course of left atrial myxoma is often progressively downhill, much more so than that of the usual case of rheumatic fever. Of the cases reviewed half of the patients had died or had had a cardiac operation within a year of the onset of symptoms. However, the occasional patient may have symptoms for 20 years or more. The cardiac manifestations may improve with therapy as was reported in one other pediatric patient[13] and occurred in the present case.

Right atrial myxomas produce postural symptoms, signs of right heart failure, tall peaked "P" waves and right bundle branch block in the electrocardiogram, and x-ray evidence of right atrial and right ventricular enlargement.[1,4] The percentage of correct diagnoses during life would seem to be much higher in myxomas situated in the right compared to those in the left atrium.

No case was found in the literature where both atria were involved to the degree present in this case, with symptoms of emboli to systemic and pulmonary systems. In one reported case[14] separate tumors were present

Table II. Major symptoms in left atrial myxoma

Symptom	*% of cases*
Dyspnea on exertion	72
Emboli	52
Edema	40
Palpitations	36
Chest pain	30
Orthopnea	21
Postural symptoms	18
Sudden death	15
Fever	12
Leg pains	9
Syncope	6
Epistaxis	6
Macular leg rash	6
Splinter hemorrhages	6

Table III. Heart sounds and murmurs in left atrial myxoma

	% of cases
No murmurs	10
Diastolic and presystolic murmur	74
Apical systolic murmur	71
Change of murmur with posture	6
Variability of murmurs	16
Loud mitral first sound	48
Loud pulmonary second sound	45
Opening snap	6
Gallop rhythm	10

Table IV. Electrocardiogram in left atrial myxoma

	% of cases
Normal	15
Right ventricular hypertrophy	46
Right axis deviation	38
Left ventricular hypertrophy	0
Low voltage QRS	8
T wave changes	23
P wave changes	27
Rhythm changes	19

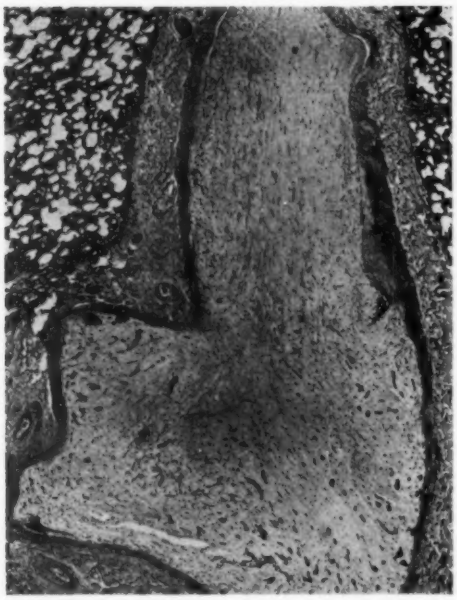

Fig. 5. Tumor embolus in pulmonary artery with capillaries growing into tumor. (Original magnification ×20.)

in both atria, and in one case of right atrial myxoma paradoxical embolism occurred through the foramen ovale.

At the time of this review at least 19 cases of left atrial myxoma have been diagnosed ante mortem, 3 by angiocardiography, 13 at operation for mitral stenosis, 2 on clinical grounds supported by heart catheterization data, and 1 by embolectomy. Eight cases of right atrial myxoma were diagnosed ante mortem, 6 by angiocardiography, 1 by observing the calcified tumor, and 1 at operation for mitral stenosis. Once the diagnosis of myxoma is thought of, angiocardiography is a simple and safe procedure, and its more frequent use should increase the number of antemortem diagnoses. Initially results at operation were disappointing, and only one patient survived a closed heart operation and blind removal of the tumor.[15] The method of choice would seem to be cardiopulmonary bypass with the use of a pump oxygenator, but hypothermia has been successfully used in over 10 cases. At the time of this review, at least 15 cases of left atrial myxoma have been successfully operated on, and 8 patients with right atrial myxoma have survived the operation.[16-19]

SUMMARY AND CONCLUSIONS

1. The tenth case of an atrial myxoma occurring in a pediatric patient is reported, and the manifestations of atrial myxoma are reviewed.

2. The most notable feature of left atrial myxoma in the young is the high incidence of cerebral emboli. Any embolic episode in a pediatric patient should suggest the possibility of an atrial myxoma, and angiocardiography should be considered, despite the absence of cardiac symptoms and signs.

3. The tumor in the present case involved both atria and symptoms from emboli in both pulmonary and systemic systems were present.

4. In the young patient, atrial myxoma may closely simulate rheumatic heart disease, and the clinical picture may be that of mitral regurgitation, rather than stenosis as is usually emphasized for adult patients.

5. In apparent cases of mitral valve disease left atrial myxoma is suggested when: (a) there is no history of rheumatic fever; (b) the intensity of the murmurs changes rapidly and often; (c) the murmurs change with posture; (d) postural symptoms occur; (e) the course is relentlessly downhill; (f) there is severe disease with persisting sinus rhythm; (g) there are emboli in the absence of atrial fibrillation; and (h) the clinical picture resembles mitral stenosis, but a systolic apical murmur is frequently heard.

6. Right atrial myxoma is suggested: (a) in isolated tricuspid valve disease, (b) in unusual cases of right heart failure, (c) when there are postural symptoms, (d) in cases with recurrent pulmonary emboli.

ADDENDUM

Since this review was completed Skanse et al. (Acta med. scandinav. 164: 321, 1959) reported the case of a 15-year-old girl with a left atrial myxoma and no cardiac symptoms who died of a cerebral tumor embolus.

We wish to thank Dr. Jan Hoogstraten for the photomicrograph, and Dr. W. May for the photographs of the fundus oculi.

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TROPICAL PEDIATRICS

American trypanosomiasis

I. Clinical and epidemiologic background of Chagas' disease in the United States

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FOLLOWING the discovery of American trypanosomiasis in Brazil by Carlos Chagas in 1909, this disease has been found in many other countries of the Western Hemisphere. Detection has followed a stereotyped pattern in each one. First, the animal reservoirs and their associated transmitting insects (the reduviid bugs) are discovered. A few infections in man are then recognized and reported. The finding of disease in humans stimulates surveys using laboratory diagnostic methods. When these unearth examples of unrecognized infection, clinical interest is excited and increased numbers of cases are discovered in humans. This pattern has occurred in many countries. Some are in the final stages of this "diagnostic evolution" and can define their problems with respect to Chagas' disease. Others are less far along such paths, and for them the extent or importance of the disease remains uncertain.

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The United States is in the latter category. Animal and insect hosts have been delineated for many years; significant infection of these has been documented in many areas of the Southwest.[1-5] Two instances of indigenous human infection have been etiologically diagnosed.[6, 7] Studies designed to detect unsuspected cases in humans have been made.[8] Nine seropositive cases have been thus revealed. Although all proved cases in human beings have been found so far in South Texas, results of current developments are possibly important enough to engage the attention of physicians in certain other regions of the United States.

The material assembled here is widely scattered in periodicals not easily available to physicians caring for children. It is reviewed with the hope that it may prove of interest to United States pediatricians and might help lead to occasional recognition of acute Chagas' disease.

NATURE AND TRANSMISSION OF CHAGAS' DISEASE

The human ailment produced by *Trypanosoma cruzi* has been generically named American trypanosomiasis. Throughout South

America it is universally called Chagas' disease to honor this man's truly unique accomplishment of discovering first the parasite and insect host, then postulating and demonstrating the animal reservoirs, and finally elucidating the human disease.

The trypanosome may infect a number of mammals besides man. Unlike its African relatives (*T. gambiense* and *T. rhodesiense*) *T. cruzi* is a pleomorphic trypanosome and has several forms during its life cycle in the mammal host. Transmission between animals is effected by a group of blood-sucking insects known as triatomiids. There are many species of these insects in the Western Hemisphere which are capable of transmitting the disease.

The insect ingests trypanosomes with a blood meal. Invading the bug's gut wall, the organism undergoes transformation and multiplication. The crithidial and infective metacycle trypanosomal forms then enter the bug's intestinal lumen and swarm in the insect's feces. These insects defecate while feeding and this habit is important for transmission of *T. cruzi*. Dejecta containing larvae in infective metacyclic form are deposited near the puncture wound and the victim, itching from the bite, may rub the organisms into it. Thus penetrating adjacent tissues, the slender metacyclic forms enter tissue cells, metamorphose into a leishmanial stage, multiply by binary fission into a leishmanial "nest," and alter into trypanosomal forms (Fig. 1). These soon emerge for future migration. They may wander locally or travel by the blood or lymph stream to invade more distant cells and repeat the process (Fig. 2). Since the insect is a night feeder, the individual is usually bitten during sleep, often on the face. In this case the larvae may reach the eye and penetrate the conjunctiva; this is a rather common portal of entry.

T. cruzi has been found in nearly every tissue; however, striated muscle (including the heart), the walls of the intestinal tract, the central nervous system, the subcutaneous tissues, and the reticuloendothelial tissues of the lymph nodes, spleen, and liver are most heavily infested (Fig. 3). Variation in the degree of tissue parasitization may result from such factors as the age of the patient (the young are more susceptible to central nervous system involvement), the biting habits of the insect, the frequency of reinfection, and tropistic differences between strains of the parasite. Strangely enough, considering the behavior of the West African trypanosomes, central nervous system involvement is relatively rare and almost always seen in infants; in adults it may occur when the inoculation is massive.

Organisms can pass the placenta and cause congenital infection.[9] The nursling may acquire infection from the mother's milk. Transmission by transfusion of infected blood has occurred.[10]

The epidemiologic relationships between animal host, insects, and trypanosomes are diagrammed in Fig. 1.

CLINICAL FINDINGS IN CHAGAS' DISEASE

Symptoms and signs begin after an incubation period of one to two weeks. Their intensity is related to the size of the inoculum and to the age and nutritional state of

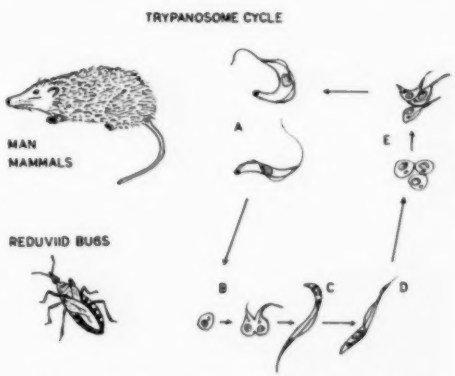

Fig. 1. The trypanosome form of *T. cruzi (A) is* seen in the blood of man and animals. When ingested by a reduviid, the trypanosome undergoes metamorphosis in the insect's gut wall to the leishmanial form *(B)*. This transforms to a crithidial *(C)* and an infective metacyclic form *(D)*. These infect the animal via the insect feces and establish leishmanial forms *(E)* in the tissue cells. These transform to the free-swimming blood trypanosomes.

Fig. 2. *T. cruzi* in the blood of the patient shown in Fig. 4. Characteristic *S* and *C* shapes; anterior flagellum, central nucleus, and posterior kinetoplast.

the patient. The variable pattern of symptoms is the result of the degree of parasitization of different tissues and the degree of structural and functional alteration produced. Some symptoms are derived from reactions to localized tissue invasion and destruction; others (e.g., cardiac) represent the cumulative functional result of structural damage. Exotoxin production has recently been claimed to be a factor in producing damage to autonomic nervous system structures.

Two stages are commonly described. The acute stage, following inoculation, wherein symptoms result from invasion of the parasite and a later chronic stage, when this effect is modified by host immunity.

Acute Chagas' disease occurs in infancy and childhood; most patients are under 10 years of age. There are two groups of effects: (1) a general host reaction to invasion by the organism and (2) those resulting from widely scattered leishmanial multiplication which signally damages organs most heavily seeded.

In the chronic stage, seen in adults, symptoms and signs are the result of a smoldering slow damage to heavily parasitized organs. Host-parasite studies seem to indicate that host resistance results chiefly from the production of local tissue antibodies. Trypanosomes, as they emerge from the leishmanial tissue nests, are apparently either destroyed or inhibited in their ability to invade the blood stream. Local reparasitization results, and organs heavily parasitized during the acute stage undergo a creeping destruction. Organs with a smaller initial parasite load may be spared further destruction, as the infection within them is smothered by a rising tide of local tissue immunity. This corrosive process is usually most manifest in the heart muscle and in the walls of the intestinal tract.

Local tissue resistance might be used to explain certain observations on the course of natural and experimental infections. Most obvious of these is that severe chronic disease seems related to reinfection. As the local immunity of the various tissues increases, newly inoculated organisms would meet this effect as they tried to enter tissues during their blood spread. Less resistant organs would again be parasitized by leishmania, their destruction accelerated. If reinoculation did not occur, the organ might achieve sufficient immunity to destroy the parasite.

ACUTE FORMS OF CHAGAS' DISEASE

Variable in its manifestations, acute Chagas' Disease is another "great imitator." So much so that, in endemic areas, any persistent febrile disease in infancy is often presumed to be Chagas' disease until proved otherwise. It would be tedious to trace out all the mimicry, but additional examples of acute Chagas' disease might be recorded if physicians in endemic areas adopted an

imaginative attitude when confronted with an infant with "virus" infection or conjunctivitis, idiopathic myocarditis or encephalitis.

The acute form may be sufficiently nondescript as to be (in endemic areas) always included in the differential diagnosis of obscure fevers. In some children the symptoms are only those of a general host-response to infection. Fever, fretfulness, irritability, headache, and some edema may constitute the entire clinical spectrum. The edema may be only facial and palpebral or may involve the legs and feet as well. Diarrhea, with occasional vomiting, is a common symptom in small infants. A mild bronchitis, with cough and scattered râles, may occur. The fever, either intermittent or continual, may range from 100 to 104° F. After several days, a fine rubelliform rash occasionally appears on the trunk and fades in a day or so. Some degree of hepatomegaly and splenomegaly usually develops within the first week. About all that the physician sees in the mild acute form is a puffy-eyed, febrile, fretful infant, perhaps with a slight cough, anorexia, some diarrhea, occasionally with an evanescent rash, and possibly slight hepatic or splenic enlargement. These findings disappear after 3 to 6 weeks and the infant apparently recovers (Fig. 4).

In such cases, the blood count may arouse suspicion of trypanosomiasis. After the first week, most infants have a leukocytosis with a lymphocytosis. The white cell count usually exceeds 18,000; it may rise to 30,000. The lymphocytes, many of them young forms, may number 70 to 90 per cent, giving a "pseudoleukemic" pattern. In very young infants eosinophilia may occur. Platelets are abundant. The parasite may be found in the blood by appropriate methods.

More severe examples of the acute "nondescript" form may be seen. Edema may be so marked and generalized as to suggest nephritis. In such instances, central nervous system involvement with convulsions produces a picture simulating nephritis with encephalopathy. In very young infants, central nervous system involvement may dominate the picture with fever, severe generalized and persistent convulsions, stupor, opisthotonus, and nuchal rigidity.

Either the reaction at the site of inoculation of the parasite or its embolic deposition in diagnostically accessible locations produces rather distinctive patterns which serve as a basis for describing the "classical" types of acute Chagas' disease. While these cases have the general systemic findings described above, additional and often more characteristic signs give the physician his clue. These relate to the multiplication or transformation of the parasite at local tissue sites.

A local reaction of variable degree, consisting of edema, induration, erythema, and slight tenderness, with occasional ulceration or necrosis, may take place at the site of inoculation and is called an *inoculation chagoma*.[11] If this is also the site of the insect bite, the lesion will commonly be found on the face or other exposed part. One can trace a biphasic course for the local lesion. The insect's bite usually produces an erythematous, papular, urticarial reaction which starts to subside in a day or so. If trypanosomal inoculation occurs, the subsiding lesion flares after several days and a localized cutaneous and subcutaneous brawny induration develops. Some inflammation is usual; ulceration and necrosis are less frequent. Within a few days the regional nodes become enlarged and slightly tender.

When trypanosomes are inoculated into the conjunctival sac, the reaction associated with flagellate multiplication occurs about the eye. Unilateral dacryocystitis, palpebral

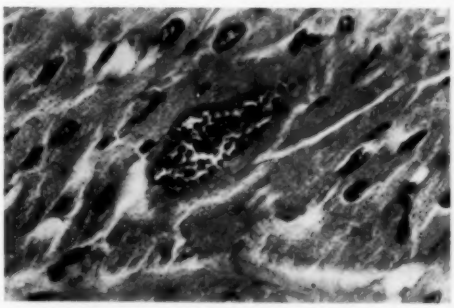

Fig. 3. Leishmania "nest" in hamster heart muscle.

conjunctivitis, and swelling and erythema of the lid occur. This combination is called *Romana's sign* after the Argentine physician who first stressed its diagnostic significance. Itching, tearing, and some mucoid drainage are present; pain is not a conspicuous feature. Tender enlargement of the preauricular node follows (Parinaud's syndrome). It is rarely seen in the first year of life; it occurs in about one third of the patients under 12 years of age and in about one-half of adult patients.

Other signs may develop as the result of hematogenous dissemination of the parasite. Peculiar to infancy is the *lipochagoma geniano* described by Jorg and Freire.[12] It is the result of parasitization of the buccal sucking pad of the nursling; painful induration and swelling of this structure lead to fretfulness and crying with sucking. The swelling and tenderness are best demonstrated by bidigital examination with one finger in the mouth. It appears 7 to 14 days after inoculation, and lasts about 30 days. Histologic sections reveal inflammatory infiltration and leishmanial nests.

Fig. 4. "Nondescript" acute Chagas' disease in 10-month-old child. Note palpebral, facial, and leg edema.

Hematogenous chagomas are metastatic lesions scattered through the subcutaneous tissues of the body, usually over the trunk and proximal extremities. They are slightly tender, indurated areas 1 to 3 cm. in diameter. They appear during the febrile stage, usually number 8 to 12, and show a histologic appearance similar to that seen in the buccal fat pads. They are most common in children under 3 years of age.[11]

Many of the symptoms and signs given in descriptions of "classical" acute Chagas' disease result from visceral involvement following hematogenous dissemination of the parasite.

Most frequent are signs indicating parasitization of the liver and spleen; *hepatosplenomegaly* is especially common in infants under 1 year. *Lung* involvement is more overt in infants, but toddlers are apt to have symptoms of bronchitis.

The frequency of *myocardial* involvement is difficult to assess from studying the literature. In the first half-year of life, acute myocardial damage may produce cardiomegaly, arrhythmias, and cardiac failure. Deaths from acute myocarditis are seen mostly in infants. The mortality rate is hard to determine but probably does not exceed 5 per cent. A sublethal degree of myocardial involvement in acute cases is suggested by such features as tachycardia, cardiac enlargement, and gallop rhythm. Prolongation of the P-R interval, low voltage QRS complexes, and S-T segment changes occur in the ECG.

Severe central nervous system involvement is seen almost exclusively in infants less than 6 months of age. Generalized convulsions are common. Signs of meningeal irritation with irritability, nuchal rigidity and opisthotonic posturing are present in less severely affected patients. Parasites may be found in the brain and meninges. Severe brain involvement leads to extensive gliosis; various residual symptoms persist in those who sur-

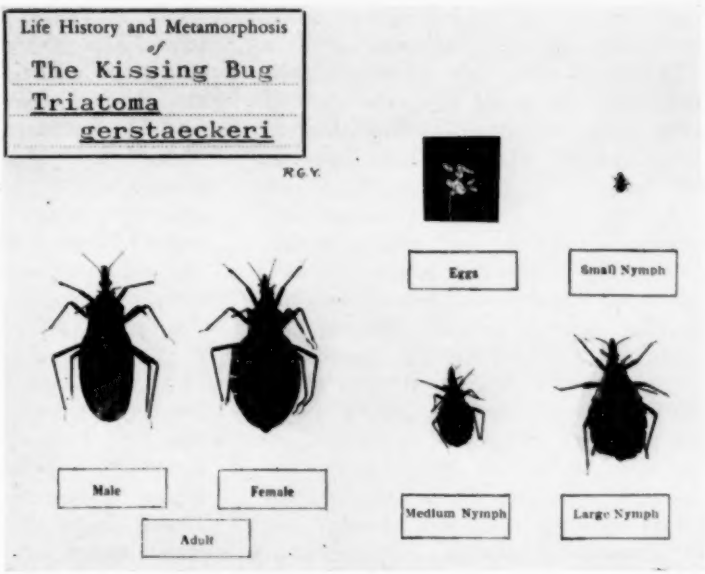

Fig. 5. The insect vector. All stages carry *T. cruzi.*

vive. The spinal fluid pressure is increased; the cell count is 15 to 20 per cubic millimeter; the protein content is slightly elevated, and there are normal levels of glucose and chlorides. The organism will rarely be seen in the spinal fluid unless a very careful search is made.* Chagas' meningoencephalitis is most dangerous and responsible for most of the deaths in infants. Data on the residual effects in those who survive are not available.

Bone marrow involvement probably accounts for the common leukemoid reactions. Intestinal involvement is thought to be responsible for the occurrence of diarrhea. In many instances the serum albumin may be reduced and the gamma globulin fraction elevated.

The majority of patients with the acute disease survive. Even in endemic areas, many patients do not come to medical attention, so that neither true incidence nor true mortality rates are known. Available statistics, based on moderate and severe cases, indicate that the mortality rate is highest in children, with one third of the deaths in the first year of life.[14, 22] Some authorities estimate that when inapparent as well as overt infections are counted, the case fatality rate would not exceed 1 to 2 per cent.[23]

*Since the trypanosome is very active and hardy, a portion of cerebrospinal fluid may be centrifuged 15 minutes at 2,800 r.p.m. A drop of sediment is placed under a cover slip and examined, without staining, for the extremely motile organisms. They are not at all fragile, and will survive at room temperature until the slide dries.

CHRONIC FORMS OF CHAGAS' DISEASE

It was long felt that acute infection invariably led to chronic disease. There is much evidence, both clinical and experimental, to indicate that this may not be the case and that recovery from the acute phase usually takes place unless reinfection occurs. From this viewpoint, intermittent episodes of fever and other symptoms seen in the latent period are interpreted as manifestations of reinfection in partially immune hosts.

Regardless of the exact mechanism, apparently from 10 to 20 per cent of acute cases in endemic areas, develop severe, often fatal, lesions in Chagas' disease. Most com-

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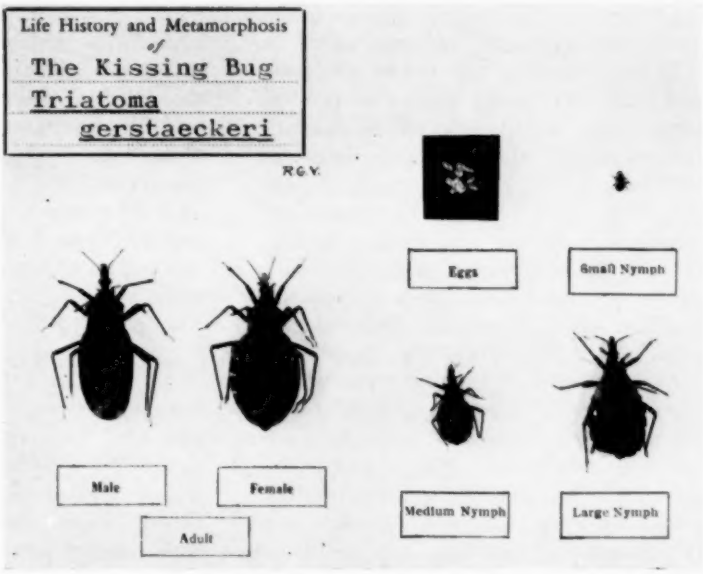

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monly these are the result of damage to the myocardium or to the intestinal walls.

The most familiar and serious is *chronic myocarditis*. Symptoms of cardiac involvement usually begin in the second or third decade, leading to more severe symptoms and death in the third or fourth decade. The clinical pattern is one of gradually advancing myocarditis and cardiac failure. Tachycardia, ventricular premature beats, cardiomegaly, and various degrees of cardiac disability may be present. Electrocardiograms usually show conduction disturbances and some degree of left ventricular strain. The most frequent electrocardiographic findings are partial or complete A-V block and complete right bundle branch block. Details of Chagas' myocarditis have been described by Rosenbaum and Alvarez[13] and Laranja and associates.[14]

In endemic areas Chagas' disease is often associated with *megaesophagus* and *megacolon*. Koberle[15] introduced the term "mega" to cover a variety of lesions and has carried out laborious studies to establish causal relationship. Not all South American workers share Koberle's views. An excellent, dispassionate study on this topic is that of Atias and his co-workers.[24] There is an interesting English review by Jung.[16]

ANIMAL VECTORS OF CHAGAS' DISEASE IN THE UNITED STATES

In this country, heaviest infections have been found in wood rats, opossums, skunks, and armadillos. Infected dogs and cats are important vectors in South America, but limited surveys here have not yet demonstrated an important incidence of infection among these animals. The raccoon has been found infected east of the Mississippi. Maps 1 to 3 show the habitats of these animals, and the heavily marked spots indicate areas where infection has been discovered. In some instances parasitization of opposums and wood rats has been heavy, comparable to that encountered in South America.

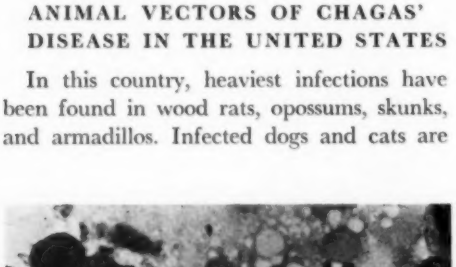


Fig. 6. Leishmanial forms in hamster spleen.

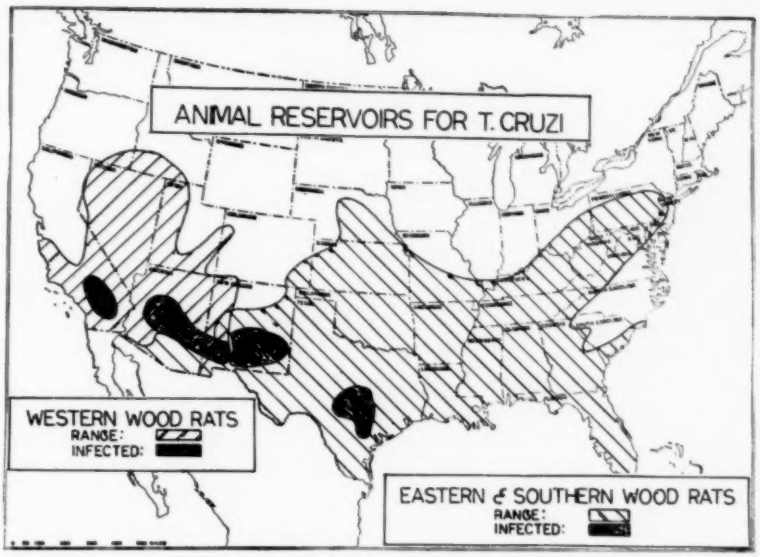
At present, animal infection has been detected in Arizona, California, New Mexico, Texas, Louisiana, Georgia, Florida, and Maryland. From the ranges of the animals involved it is evident that mammalian infection is potentially widespread in the United States; actual extent of such infection east of the Mississippi is not known.

Even a heavy animal parasitism is not important to humans so long as the animals live apart from man. However, opossums and wood rats do not leave their haunts when land is cleared. Clinging to their patrimony, they continue to nest in and around dwellings in rural and suburban areas. This behavior brings them into closer and closer contact with man and makes them increasingly important as animal reservoirs as suburbanization continues in our country.

INSECT VECTORS OF T. CRUZI IN THE UNITED STATES

A number of blood-sucking arthropods can be infected with *T. cruzi* but the only epidemiologically important ones are those belonging to the *Triatominae* group of reduviid bugs. The ranges of the more common United States species of this insect are shown on Map 4; areas naturally infected with trypanosomes are localized. Rates of infection of the insects in these areas have been high (20 to 90 per cent) and are comparable to those of endemic areas of South America.

These insects live on the blood of vertebrates. They live intimately with the animals in their nests and burrows. They are not gourmet types and readily feed on almost



Map. 1. These creatures, like the opossum, will nest in human habitations and are probably the most important reservoir in the Western United States.

any warm-blooded creature they can get their suckers into. Both adults and nymphs can carry *T. cruzi*. Only the adults fly, however, and the nymphs remain close to animal burrows or nests. They will also infest houses when the animals live nearby and are especially pesky for the human occupants when the animals are driven out and the hungry insects are left behind. They feed at night and generally shun light, hiding in dark cracks and crevices by day. When a light is made at night they scurry rapidly out of sight. Their bite is practically painless and will not disturb most sleepers. They usually feed on exposed areas—the head and extremities. All species defecate during the feeding, leaving sooty, black smudges on the skin. Various amounts of local irritation and itching occur from the bites. Large local reactions may develop on the skin of some persons and are thought to be related to sensitization from prior bites.

All the U. S. A. species are sufficiently like *Triatoma gerstaeckeri* (Fig. 5) so that it may stand as a model for the group. This is the most common Triatoma of South Texas.

Persons who have been bitten will instantly recognize the insect and call it by some local term: "blood-suckers," "chinche del monte," "wild bedbug" and "Mexican bedbug" are the "nicknames" most commonly employed in Texas. Elsewhere they have been called "kissing bugs."

As with animals, high rates of parasitization observed, although impressive when compared to South American rates, are not meaningful unless human biting occurs.

Conversely, recognition of the insect by patients and a definite history of house infestation and of frequent bites is probably the strongest historical evidence favoring Chagas' disease in clinically suspected cases.

DIAGNOSIS OF CHAGAS' DISEASE

As is evident from the foregoing, clinical suspicion should be aroused when an infant or child, residing in an endemic area, develops a persistent or irregular fever in association with one or more of the following:

Edema, facial or pedal, without urinary abnormalities.

Unilateral conjunctivitis with preauricular lymphadenitis.

Cellulitis and induration at the site of an insect bite.

Otherwise unexplained hepatosplenomegaly.

Tenderness and swelling of the buccal fat pad in nurslings.

Tender, indurated subcutaneous nodules.

"Nonspecific" myocarditis.

Meningoencephalitis.

Leukocytosis and lymphocytosis.

If there is also a history of having recently been bitten by a Triatoma, vigorous attempts should be made to isolate *T. cruzi*.

Although *T. cruzi* trypanosomes are present in the blood during the acute stages, they are not always easily demonstrated, especially after the fever has subsided. In the more severe cases during the febrile period the blood is almost literally swarming with trypanosomes, and they are readily identified by three simple examinations*:

1. Wet coverslip preparation. This is made by placing a drop of blood (plain, citrated or heparinized) on a slide and covering it with a cover slip. Under low-power magnification the frenetically motile trypanosomes may be seen jostling their way among the red cells. Brought under high power, the organism is seen to have a "snapping" kind of twisting and turning motion.

2. Thick film preparations from the buffy layer. These are made from citrated or heparinized blood which has been spun down in a Wintrobe hematocrit tube. A portion of the buffy layer is set up as a wet preparation and examined for motile forms. If none are seen, thick film smears are stained with Wright or Giemsa stains. At least three such films should be searched with oil immersion. The stained organism is characteristically C or S shaped (Fig. 2); the cytoplasm is stained blue, and the nucleus and kinetoplast are stained red or pink.

3. Phytohemagglutination-concentration test. This test is technically more involved, but quite practical. It consists of the application of a substance to agglutinate and remove red blood cells. Since larger aliquots of blood can be studied, it has value when the parasitemia is low. This method has not yet had wide clinical application but should be employed by any laboratory that is frequently faced with the problem of isolating trypanosomes.[17]

Thorough and competent search by these methods on successive days and during times when the temperature is elevated will usually reveal parasites. Failure to find *T. cruzi* by direct methods does not exclude infection, and more complicated means of demonstration may then be undertaken. These require trained personnel and unusual facilities.*

Clinically *acute cases* may yield trypanosomal isolations by one of three techniques:

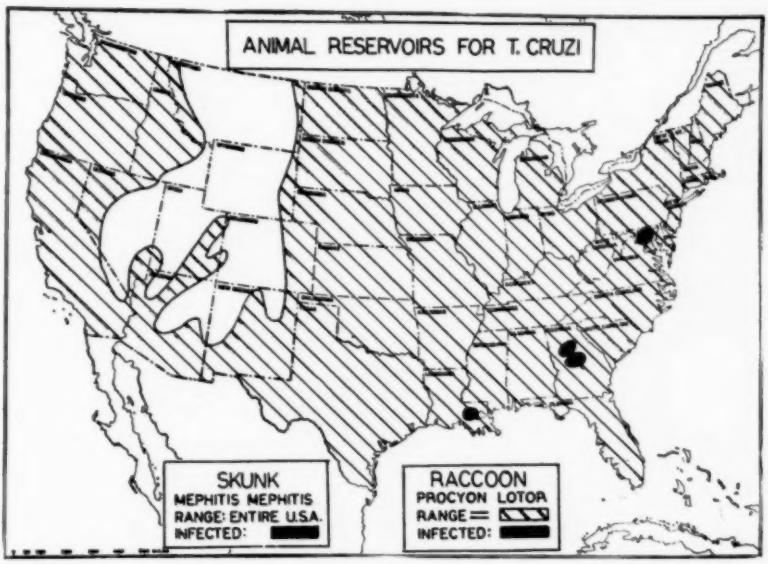
1. Blood culture. One milliliter of fresh or heparinized blood should be inoculated on slants of NNN medium in screw-cap culture tubes. At least four tubes should be inoculated. They are then incubated in a cool, dark place. They may be checked after 2 weeks, but they should not be discarded as negative until after 90 days.

2. Xenodiagnosis. This requires a colony of laboratory-reared triatomes. Both a direct method (where the insects feed on the patient) and an indirect technique (where they are fed heparinized blood) can be used.[18, 19] In either case, within 60 days, if trypanosomes have been consumed with the blood, the organism will have multiplied in the gut and can be demonstrated in feces of the insects.

3. Animal inoculation. Young animals are most susceptible. Hamsters and laboratory rats

*Caution is necessary when material containing *T. cruzi* is handled. It is an extremely vital animalcule and has been known to remain alive and infective in refrigerated, citrated blood for as long as 8 months. Blood from suspect cases should be handled with respect. It is good practice to rinse syringes, needles, and other utensils with 70 per cent alcohol after use and before allowing them to be handled by untrained personnel. Similar precautions should be taken with spinal fluid, fecal droppings from infected insects, and cultures and tissues from infected animals.

*Physicians desiring such diagnostic help with clinically suspicious cases may write or phone the authors at the Department of Pediatrics, Tulane Medical School, 1430 Tulane Ave., New Orleans 12, La. Telephone 524-7611, Ext. 241.



Map 2. *T. cruzi* hosts in the Eastern United States. They avoid human habitations and are probably less important as reservoirs than the opossum.

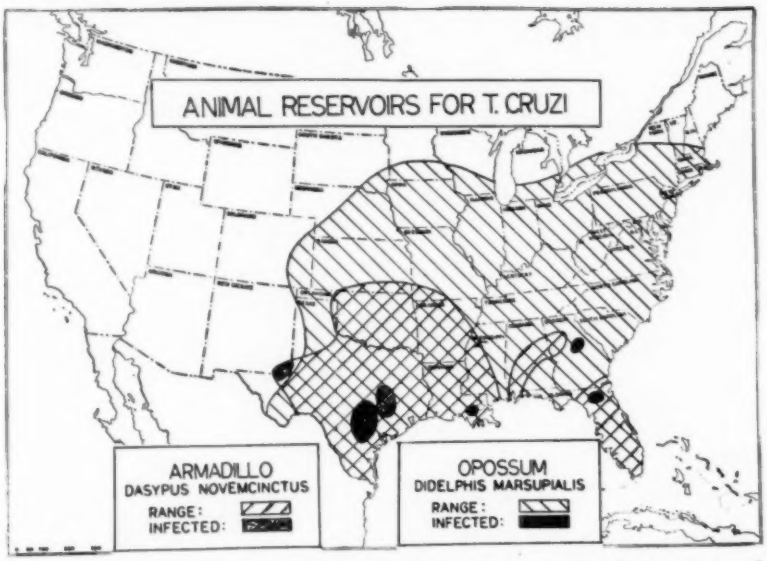
may be used as well as guinea pigs, puppies, and kittens; blood is injected intraperitoneally. Parasitization is enhanced if 2.5 mg. of cortisone is injected at the same time. Blood is periodically checked for a span of 60 days, beginning 2 weeks after inoculation. If no parasites are found, the animal should then be killed and sections of heart, spleen, and liver examined for leishmanial forms (Fig. 6).

Chronic cases may occasionally be detected by any of the last three routines, although isolations are rarely made. In such instances, or for survey of contacts, complement fixation is the most reliable test. Demonstrable antibodies for *T. cruzi* are thought to be present and reasonably persistent about 60 days after infection. An excellent, though technically formidable, test has been devised by de Freitas and Almeida.[20] Significant titers by this method, when coupled with compatible past and present epidemiologic and clinical patterns, can probably be taken as sufficient evidence of chronic or past infection. Biopsy and necropsy material may finally yield a diagnosis. Leishmanial forms have been reported from chagomas, from the conjunctivae in cases with Romana's sign, and from regional nodes, heart muscle, liver, spleen, and the smooth muscle of the intestinal wall. Adequate examination of such material can be very tedious; as many as a hundred sections may have to be searched to establish a diagnosis of chronic Chagas' myocarditis.

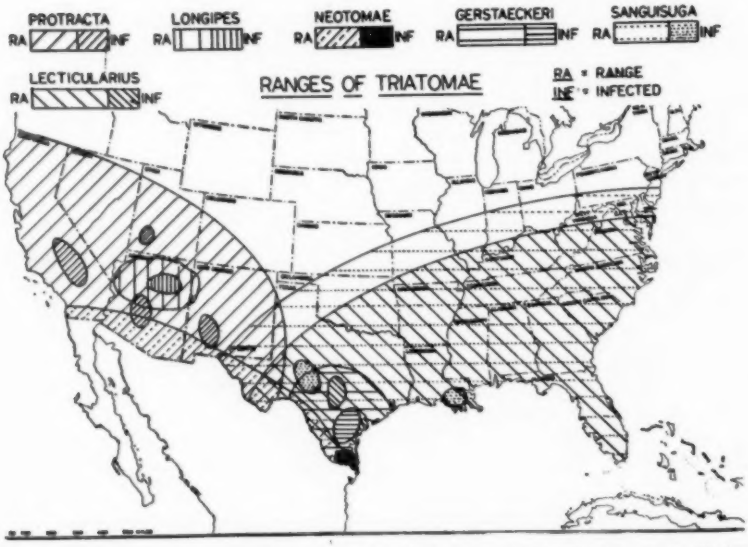
TREATMENT

There is at present no specific therapy for this infection. Agents effective for other trypanosomes or leishmanias have failed to cure the disease. Both Bayer 7602 AC (4:6 diamino-quinaldine) and primaquine have had wide use in treating patients with the disease. They are said to be effective against the trypanosomal blood forms but not the leishmanial tissue forms; i.e., they have a suppressive but not a curative action. In view of their toxicity and questionable therapeutic value, it is probably wise to use them only in instances of severe acute Chagas' disease.

Definite clinical and experimental evidence exists to show that steroids and chlortetra-



Map 3. The armadillo generally avoids humans. The opossum remains in towns and suburbs, nesting in and around homes and outbuildings. He is, therefore, an important reservoir over the Eastern and Southern United States.



Map. 4. Ranges and areas of documented infection for the six most common United States triatomes. Opportunity for human infection is greatest in California, Arizona, New Mexico, and Texas. Little attention has been paid to insect infection in the Eastern states, an important consideration now that animal infection has been found there.

cyclines exacerbate the infection and should not be used.

Symptomatic and homeostatic treatment is important. Associated bacterial and parasitic infections are frequent in acute Chagas' disease and may be a factor in susceptibility. These should be managed by appropriate measures. Protein and vitamin deficiencies have been documented as conditioning factors related to diminished host resistance and should be vigorously corrected.

Reinfection must be avoided. Animal nests should be eradicated and the dwelling protected against wood rats and opossums. The triatomes may be killed by dieldrin (2.5 per cent emulsion) or lindane (1 per cent in hydrocarbon base). The toxicity of these insecticides should be kept in mind. These agents may not kill the eggs and require repetition after 2 to 4 weeks as new insects hatch.

SUMMARY

Most United States physicians are likely to think of American trypanosomiasis as a remote and dramatic tropical illness. Accumulated evidence suggests that it is quite likely to occur in certain areas of this country as a rather nondescript, self-limiting, or even lethal febrile disease of infants.

For the physician puzzled by an infant with an obscure febrile illness, the most important single clue to Chagas' disease is a history of home infestation by, and bites from, triatomiid bugs. In such a situation, a vigorous effort should be made to demonstrate *T. cruzi* in the patient's blood; if this effort fails, other diagnostic procedures are described which may prove effective.

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Juvenile delinquency, 1959

During 1959 1.7 per cent of all children aged 10 through 17 years were handled by the juvenile courts as delinquents, according to a report issued by the Children's Bureau. About 15 per cent of these committed more than one offense. Though the number of delinquency cases increased in 1959 over the previous years, the increase was the smallest in the past decade and was considerably less than the 5 per cent rise in the child population.

Actually the number of cases handled by the juvenile courts in urban areas decreased by 2 per cent while the cases in semiurban and rural areas rose by 7 and 15 per cent, respectively. The trend toward a more rapid increase in juvenile delinquency in rural areas which has been going on for a number of years is continuing. The semiurban and rural courts, however, handle only about two fifths of all the court delinquency cases in the country. The delinquency rate (the number of cases per 1,000 child population aged 10 through 17) is still three times as great in predominantly urban areas as in predominantly rural areas.

Almost half of the cases included in the Children's Bureau report were handled unofficially. The proportion was higher in urban than in rural courts, owing, perhaps, to the availability of ancillary agencies in the urban courts.

Until 1957 traffic violations were included with other juvenile delinquency offenses. This is no longer the case. Consequently, statistics on juvenile delinquency since 1956 are not comparable with earlier data.

Juvenile court statistics, 1959, United States Department of Health, Education and Welfare, statistical series No. 61.

MEDICAL PROGRESS

The effect of the atmospheric environment on the premature infant

William A. Silverman, M.D.*

NEW YORK, N. Y.

CONSTANTIN P. YAGLOU was born of Greek parents in Turkey on Jan. 26, 1896. Upon graduation from Robert College in Constantinople, he came to the United States, entered Cornell University, and received a Master's degree in 1920. In 1921 he joined the staff of the Research Laboratory of the American Society of Heating and Ventilating Engineers in Pittsburgh and worked with them until 1925.

Dr. Kenneth D. Blackfan of the Children's Hospital, Boston, had asked the Department of Industrial Hygiene at the Harvard School of Public Health for help in constructing and operating an air-conditioned room for premature infants. Professor Yaglou who had developed the Effective Temperature Scale while at the Research Laboratory was invited to join the staff of the School of Public Health in 1925 to take charge of this room which would stabilize the infants' body temperature.

From the Babies Hospital and Department of Pediatrics, Columbia University, College of Physicians and Surgeons.

Constantin P. Yaglou Memorial Lecture, delivered on Nov. 21, 1960, at the Harvard School of Public Health.

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This work was described fully by Blackfan and Yaglou[1] in 1933 and attracted great interest. As equipment improved, it became apparent that the same results could be attained by individual cribs, each air-conditioned. The thermal and physiologic principles established by Professor Yaglou in the first room remained valid. These principles greatly influenced the survival rate of premature infants.

Professor Yaglou's later work related to climatic preferences of people, ventilation, and air conditioning of ships and studies of habitability of climatic extremes. He carried out extensive research projects for the Armed Forces before and during World War II and was commissioned a Commander in the Navy during World War II.

He received an honorary Master's degree from Harvard University in 1947.

On June 3, 1960, Professor Yaglou died suddenly at his home in Belmont. He is survived by his wife, Jane, a son Edward, two grandchildren, a brother, and his mother.

As a pediatrician interested in the well-being of premature infants, I am particularly grateful for this opportunity to pay tribute to Professor Constantin P. Yaglou and to

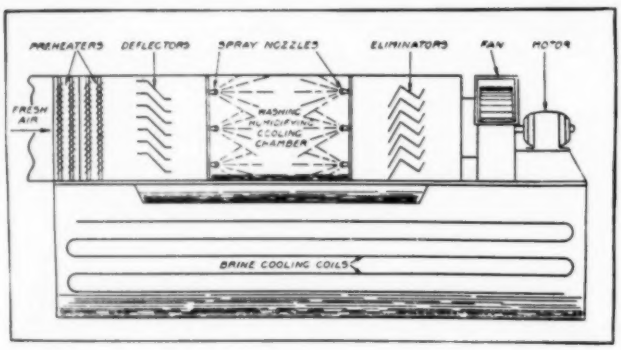

Fig. 1. Diagrammatic sketch of the central air-conditioning apparatus. (From Blackfan and Yaglou: The Premature Infant, Am. J. Dis. Child. 46: 1175, 1933.)

reaffirm the importance of his contributions to our knowledge concerning the effects of the physical environment on these very small displaced persons.

In a classic monograph published in November of 1933,[1] Dr. Kenneth D. Blackfan of the Department of Pediatrics, Harvard Medical School, and Professor Yaglou of the Department of Industrial Hygiene, Harvard School of Public Health, described the results of systematic studies of the effects of varying atmospheric conditions on vitality and growth of 352 premature infants admitted to the Infants' Hospital during a six-and-one-half-year period from June, 1923, through December, 1929. For the first two and one half years the nurseries of the Infants' Hospital were not equipped with special devices to control environmental conditions; 123 premature infants were admitted during this period. Following this a complete air-conditioning system was installed; 229 infants were admitted in the next 4 years.

The air-conditioning system had been designed by Professor Yaglou to provide accurate control of air movement, temperature, and humidity in 2 nurseries for premature infants, accommodating a total of 12 infants, and in a third observation nursery that accommodated 12 to 16 infants who had a variety of specific conditions (e.g., congenital malformations, etc.). Fig. 1 shows a simplified sketch of the central air-conditioning apparatus. Outdoor air was drawn by fan suction, passed over preheaters, and routed through a spray chamber to wash out coarse dust particles and to adjust the humidity of the air by controlling the temperature of the spray water. Droplets of water and dust carried into the air stream from the spray chamber were caught by impingement against eliminator plates. Air was then forced into the 3 study rooms, passing over individual heaters just before entry. In summer warm and humid air was cooled and dehumidified by contact with cold water in the spray chamber. The spray water was cooled by permitting it to trickle over cold brine-filled pipes in a lower section of the apparatus.

The conditioned air entered each room near the ceiling (Fig. 2) and after circulating across the room it was withdrawn near the floor by an exhaust fan. The equipment had sufficient capacity to produce 25 changes of air per hour. In each of the 3 rooms the movement of air about the cribs was approximately 15 ft. per minute. It was possible to adjust the device to obtain a wide range of air temperature and specific humidities. Continuous permanent records of dry and wet bulb temperatures were kept for the duration of the clinical trials.

Using these facilities, Blackfan and Yaglou made extensive observations on the physiologic responses of full-term and premature subjects in varying environmental conditions. They also set out to determine the optimum environmental temperature and humidity for premature infants. At first relative humidities of 20 per cent and 80 per cent were studied but it was found that humidities above 65 per cent were distressing to the nurses and that symptoms of dehydration occurred fre-

quently in premature infants when the humidity was kept below 30 per cent for a prolonged period. As a result of these experiences the authors decided to study the effects of prolonged exposure to 30 per cent relative humidity, referred to as low humidity, and to 65 per cent relative humidity which was called high humidity. The actual ranges achieved were 25 to 49 per cent relative humidity in the low condition and 50 to 75 per cent relative humidity in the so-called high-humidity environment. To avoid confusion in the discussion which follows, I will hereinafter refer to the latter atmospheric condition as "moderate humidity."

Blackfan and Yaglou observed that when premature infants were alternately exposed to the two contrasting air conditions for a week at a time, there were no obvious effects. However, after prolonged exposure to low humidity, there were definite consequences. When infants remained in environments of low humidity for two weeks or longer, they frequently developed diarrhea, body temperature became less stable, the rate of weight gain was reduced, and deaths increased. It was particularly interesting that for infants weighing less than 5 pounds the gain in weight was greater in moderate than in low humidity, whereas the reverse was true for the group of infants weighing more than 5 pounds (Fig. 3). To the best of my knowledge this paradoxical phenomenon has not been studied in any greater detail, and a satisfactory explanation is not available.

From the results of 6½ years of study Blackfan and Yaglou concluded that 65 per cent relative humidity appeared to be the air condition which was best suited to the survival and welfare of small premature infants. They suggested that the optimum humidity might be higher but 65 per cent relative humidity was considered to be the upper limit which was then practicable. This recommendation was widely accepted and for a period of almost 20 years 65 per cent relative humidity prevailed in nurseries for premature infants in the United States and in other Western countries.

Following World War II a number of developments took place which resulted in a marked change in the atmospheric conditions surrounding premature infants. The development of modern incubators made it possible to achieve high concentrations of oxygen. It soon became routine to maintain premature infants in environments of high oxygen content for prolonged periods of time in order to convert their irregular and periodic respirations to a regular rhythm. Since it was known that the drying and irritating effects of oxygen on the lungs could be ameliorated in humid environments, it seemed quite logical to provide liberal humidification of incubators as an adjunct to oxygen therapy. In the early 1950's there was considerable clinical interest in the respiratory performance of premature infants. Many of these newborn infants breathe rapidly and with apparent difficulty which is similar to that of older infants and children who have obstructions of the respiratory airway. Clinicians reasoned that since the symptoms of croup and bronchiolitis appeared to abate with the inhalation of water vapor, prema-

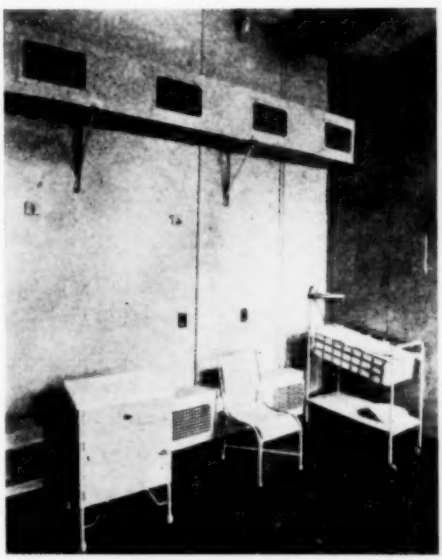

Fig. 2. Supply (top) and exhaust (bottom) ducts in the nursery for premature infants. (From Blackfan and Yaglou: The Premature Infant, Am. J. Dis. Child. 46: 1175, 1933.)

ture infants with similar symptoms might benefit from the same treatment, and mist therapy was widely applied. Later the use of a detergent solution was advocated for nebulization into the incubators of premature infants to improve the wetting action of the water aerosols.

This was the state of affairs in 1954 when Dr. Clement A. Smith[2] was moved to comment that "the sight of a small infant surrounded by a fog of vapor . . . symbolizes the present status of . . . [the] subject, which is essentially a very small body of facts enveloped in a misty atmosphere of speculation, which is walled off from its surroundings by a rigid container of prejudice." The walls came tumbling down soon after this when it was demonstrated that retrolental fibroplasia was caused by prolonged exposure to high concentrations of oxygen. The pediatric world was so shaken by the denouement that many doubts and questions were raised concerning the other conditions of the atmospheric environment surrounding the premature infant. As one reviewed the situation at this time it was apparent that since Blackfan and Yaglou's investigation there had been no critical studies of the newly introduced environmental conditions. Moreover, the Boston observations were concerned with infants over 1 week of age; there were few systematic studies of environmental influences in the first 5 days of life.

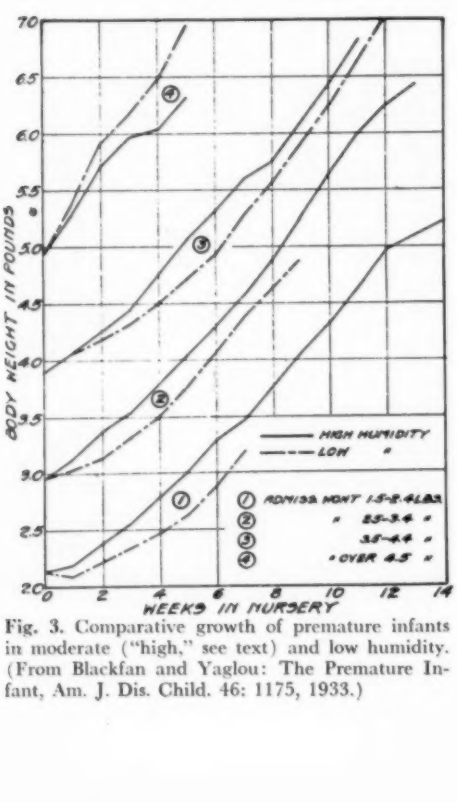

Fig. 3. Comparative growth of premature infants in moderate ("high," see text) and low humidity. (From Blackfan and Yaglou: The Premature Infant, Am. J. Dis. Child. 46: 1175, 1933.)

We undertook some studies of these questions in the premature nursery of the Babies Hospital using the technique of the controlled clinical trial. In the first trial conducted in 1953-1954[3] we compared the relative effectiveness of a detergent-treated mist atmosphere as opposed to 90 per cent relative humidity during the first 3 days of life after premature birth. On the basis of previous experience we decided that we would be willing to accept the detergent mist as superior if it succeeded in lowering the mortality rate of premature infants from 25 per cent to 15 per cent. For this reason we planned a fixed sample-size trial of 200 infants who were assigned to detergent-mist and control groups in predetermined random order. The assignments were placed in sealed envelopes so that there was no advance knowledge of the treatment category to which each infant was allotted at the time of admission to the nursery. At the conclusion of the trial 105 infants had been assigned to the detergent group, 95 to the control category. It was established that the random order of assignment resulted in two groups that were reasonably similar with respect to a number of characteristics that might influence survival. As a result one could be fairly confident that any observed difference in survival rates could be ascribed only to the environmental conditions which were on trial. However, we found that the survival rates were essentially the same in the two groups and that the distributions of necropsy findings among those who died were likewise not significantly different. As a result we concluded that there was no therapeutic benefit that could be credited to detergent mist in the first 3 days of life and we discontinued the use of this material in the nursery.

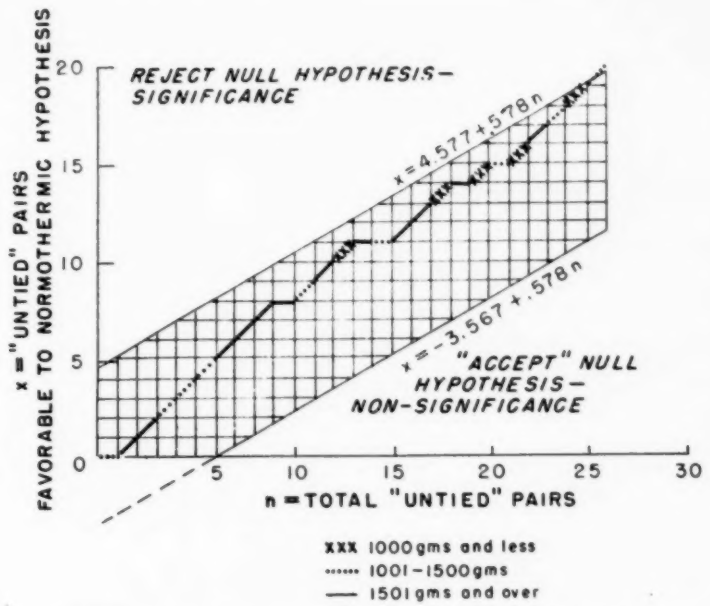

Fig. 4. Sequential plan to evaluate a difference in survival in two conditions of environmental temperature (From Silverman, Fertig, and Berger: The Influence of the Thermal Environment Upon the Survival of Newly Born Premature Infants, Pediatrics 22: 876, 1958.)

A second trial[4] was conducted in virtually the same manner as the first. Nebulized water mist was compared with 90 per cent relative humidity in the first 3 days of life. The results of this trial were the same as those in the detergent-mist trial, and we abandoned the use of all aerosols in the incubators for premature infants.

We conducted a third clinical trial[5] which was designed to bridge the gap between Blackfan and Yaglou's recommendation of 65 per cent relative humidity and the newer more humid environments that were introduced to reduce the drying effects of high concentrations of oxygen. This seemed reasonable since high concentrations of oxygen were now only rarely used and there had been relatively few reported observations of the "acute" effects of varying conditions of humidity on premature infants in the first few days of life. The humidity study differed from the first two trials in that the incubators were kept 5° F. cooler and the conditions were maintained until the infants were 5 days old. Thus all incubators were set at an air temperature of 84° F. (83 to 85° F.); in high-humidity incubators the relative humidity ranged between 80 and 90 per cent, in moderate humidity between 30 and 60 per cent. At the conclusion of this trial we noted that the survival rate during the trial period among infants who were in 80 to 90 per cent relative humidity was significantly higher than the rate of the controls. In each birth-weight group the proportion of survivors was greater in the more humid incubators, but the largest differences occurred among infants whose birth weight was below 1,501 grams (Table I).

It was not clear how this difference in survival had been achieved. The frequency distribution of necropsy findings among infants who died in the contrasting groups were essentially the same, and the incidence and severity of respiratory symptoms were not different among the survivors. As we puzzled over the meaning of these observations we re-examined Blackfan and Yaglou's

Table I. Survival rates by birth weight in two conditions of humidity. Air temperature 84° F. (83° to 85° F.)

Birth weight (grams)		*Relative humidity (%)* 80-90	30-60	*Difference*
≧ 1,501	No.	71	70	
	Survived	80%	74%	6%
1,001-1,500	No.	73	71	
	Survived	82%	65%	17%
≦ 1,000	No.	20	19	
	Survived	55%	37%	18%
	Total	164	160	
		78%	65%	13%

report and wondered if our results could be explained on the basis of phenomena which they observed in 1933. From their work we expected that at any given air temperature infants in high humidity would have higher body temperatures than a control group in less humid environments. This was true of the average body temperatures of infants who were enrolled in our trial, the differences between the means varied from ½° F. in the largest infants to almost 2½° F. in the smallest infants. At this point we asked whether the infants in the more humid incubators survived in greater numbers because they were warmer than the controls.

In an attempt to evaluate thermal influences on survival in the first 5 days of life we undertook a fourth clinical trial.[6] Two air temperatures were chosen for contrast: 84° F., the temperature used in the humidity trial just completed, and 89° F., the temperature used in the first two mist trials. The relative humidity was 80 to 90 per cent in both sets of incubators. This resulted in a slight, and in our judgment unimportant, difference in the specific humidities. The conditions of the trial were maintained until each infant reached the age of 5 days.

In this trial random pairing was carried out within birth-weight groups. One member of the pair was assigned to a warm incubator, his match to a cool incubator. The order of allocation was predetermined and assignment stickers were placed in sealed envelopes. We chose a modification of the method of sequential analysis to evaluate the differences in survival under the two trial conditions and this allowed a running analysis of the matched pairs as they were completed. The testing plan was set up to be sensitive to a 5 per cent improvement in survival above that experienced previously by infants in cool incubators and high humidity. In addition the standards of protection against errors of the first kind and second kind were set at 5 and 10 per cent, respectively. Using these values, Professor John W. Fertig and Dr. Agnes P. Berger of the School of Public Health, Columbia University, derived the equations of the two parallel lines plotted in Fig. 4. The outcome of pairs were classified as "tied" or "untied." Pairs in which both members lived or both died were considered "tied" in the sense that these pairs did not contribute to a decision on the question, "Are warm incubators better than cool incubators?" Pairs in which only 1 of the 2 individuals lived were "untied," and it was the outcome of these pairs which were utilized in the sequential scheme. As can be seen in Fig. 4, in the first untied pair completed in the trial, the infant in the warm incubator died and his match survived. This result was plotted horizontally in the first box. A continuation of this trend would lead to acceptance of the null hypothesis (i.e., no significant improvement of survival in warm incubators). In each of the next 8 untied pairs the infant in the warm incubator lived, the match died. A continuation of this trend would lead to rejection of the null hypothesis. As the trial progressed, it was the latter trend which prevailed and with the completion of the twenty-sixth untied pair a decision was reached. To obtain the 26 discrepant pairs, it was necessary to enroll 182 individuals, 91 pairs of infants. Of these 65 pairs were tied, in 56 both lived, and in 9 pairs both died. Of the 26 untied pairs, 20 favored rejection of the null hypothesis since in each of these pairs it was the individual in the warm incubator who survived. Eighty-four per cent of 90 infants in warm incubators survived the trial period as compared

with 68 per cent who survived in cool incubators.

We concluded that these results supported the judgment made at the end of the humidity trial that the beneficial effects of high humidity were mediated through a reduction in heat loss. However, this did not exclude the possibility that there might be an additional extrathermal influence of humidity. At present we are conducting a clinical trial which was designed to evaluate the latter contingency. The body temperature of infants in the present investigation is controlled by an infrared device which automatically compensates for the thermal influence of humidity. Thus we have been able to place infants in high and moderate humidities (80 to 90 per cent relative humidity versus 30 to 60 per cent relative humidity) but this time the body temperature of infants in both groups is the same. Using a two-sided sequential plan to evaluate the differences in survival, we have already crossed one decision line and have accepted the conclusion that there is *no* apparent beneficial extrathermal influence of high humidity in the first 5 days of life. The trial is continuing in an attempt to decide between the possibilities that (1) there is no difference between high and moderate humidity, or (2) that there is a harmful influence of high humidity.

At the present time, the question concerning the thermal environment is one of the most intriguing problems which confronts those interested in the care of premature infants. We have suggested that survival in the neonatal period can be improved when warmth is provided for these infants. Brück's[7] studies of the energy metabolism of premature infants in the first few days of life also suggest that the "optimum" temperature for these subjects may be afforded by an environment which provides an ample supply of heat and thus makes the smallest metabolic demand. The precise relationships between body size, age, and "neutral" environmental temperature will undoubtedly be clarified in the very near future.

With regard to humidity I have attempted to review our experiences in the past few years. As can be seen we have traveled very far since 1933. Our only difficulty stems from the fact that the route has been a circular one. Blackfan and Yaglou suggested that moderate humidity, approximately 65 per cent relative humidity, is the optimum environmental condition for small premature infants. In 1960 we can only add, "Amen."

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CLINICAL PATHOLOGICAL CONFERENCE

THE CHILDREN'S HOSPITAL MEDICAL CENTER, BOSTON, MASS.

Sidney Farber, M.D., Editor
Gordon F. Vawter, M.D., Assistant Editor

FOLLOWING a normal pregnancy and delivery with a birth weight of 7 pounds, 10 ounces, this boy did well until he was 2 weeks of age, when "white specks" were noted on the lips and over the buccal mucosa. This was diagnosed as moniliasis and the patient received therapy with Mycostatin. The lesions cleared and the patient did well until he was 20 days of age, when he was admitted to an outside hospital with a diagnosis of croup and pneumonitis. Scattered inspiratory rhonchi were heard throughout the chest. His throat was markedly erythematous and cultures grew out *Staphylococcus aureus,* but were negative for Candida. A faint subsiding erythematous maculopapular rash was present on the face and abdomen. The child received therapy for three days with penicillin and streptomycin, followed by 3 days of therapy with Declomycin. After six days, Mycostatin was added. Multiple ulcerated areas were then noted on the upper lips and gums, from which Staphylococcus was grown and "which looked more like herpes than thrush." At this time, the patient was noted to be lethargic and he developed a fever for the first time (102° F.). The fever was stated to be "intermittently present" throughout the remainder of the hospital stay. X-ray of the chest showed "more definite evidence of the inflammatory infiltrate first noted on admission in the right lower lobe." Erythromycin, 50 mg. per kilogram per day, and chloramphenicol, 30 mg. per kilogram per day for the next four weeks, were administered orally at the outside hospital. He remained lethargic, fed poorly, and did not gain weight. The infiltrative process was noted on the x-ray to spread throughout both lungs. A throat culture now grew out *Pseudomonas aeruginosa.* Leukocyte count was 22,000 per cubic millimeter with 18 per cent band forms. A culture was negative for fungi in the throat.

At 2 months of age, the patient was transferred to The Children's Hospital Medical Center, where physical examination revealed a poorly nourished, chronically ill, 7 pound, 2½ ounce child with cyanosis of the lips and nail beds. The temperature was 102° F., pulse, 188 per minute, respirations, 64 per minute, with marked respiratory distress. Raw excoriated areas were noted over the skin, about the mouth, and in the perianal area. The pharynx appeared injected. There was a copious purulent nasal discharge. Coarse râles were heard diffusely throughout the lung fields. The liver edge

was palpable at 4 cm. and the spleen was palpable at 1 cm. The Moro reflex was fair. X-ray examination showed that the lungs were greatly increased in volume, and throughout each lung there was hazy accentuation of interstitial markings, particularly prominent in the posterior third of each lung. The changes were consistent with a diffuse pneumonitis. Subsequent chest films were interpreted as showing that the diffuse peribronchial and interstitial inflammatory changes persisted unchanged. Multiple cultures of the nose and throat grew *Ps. aeruginosa*. A culture of a needle used in lung puncture revealed no growth and was negative for fungi. The patient at first received chloramphenicol and erythromycin for 10 days, and then novobiocin was added. These were discontinued and streptomycin, and later Coly-Mycin, was used when indicated as the drug of choice by the sensitivities of the Pseudomonas. After the child received Solu-Cortef intravenously during the second hospital week, prednisone, 2.5 mg. per day, was started on the fourteenth hospital day and continued throughout the patient's hospitalization. Mycostatin was also given. Yellow-green purulent discharge from both eyes appeared on the eighteenth hospital day, and persisted despite treatment with Neo-Cortef ointment. Finally, the corneas became opaque.

The patient continued to do poorly, with cyanosis and respiratory distress prominent, although he was being kept in oxygen and mist. The excoriating perioral and perianal skin lesions were treated with zinc oxide and Mycostatin ointment, but spread further over the cheeks, buttocks, scrotum, and thighs, while the skin of the digits also peeled. The child died after 3 weeks of hospitalization.

The hemoglobin was 11.8 Gm. per cent, leukocyte count 25,650 per cubic millimeter with 24 per cent polymorphonuclear leukocytes, 20 per cent band forms, 5 per cent metamyelocytes, 42 per cent lymphocytes, 6 per cent monocytes, 2 per cent eosinophils, and 1 nucleated red blood cell. Subsequent white counts were between 25,000 and 57,000, with 11 to 40 per cent polymorphonuclear leukocytes and 17 to 35 per cent band forms. The urine showed: albumin 200 mg. per cent, no sugar, no acetone, 5 to 12 red blood cells, and 2 to 5 white blood cells, and occasional epithelial cells. The stool trypsin was 4 plus, three times.

The electrolytes in the sweat were: sodium 23.9 mEq., potassium 30.3 mEq., and chloride, 23.8 mEq. per liter.

Serum electrolytes on the ninth hospital day were: sodium 128 mEq. per liter, potassium 7.1 mEq. per liter, chloride 81 mEq. per liter, and carbon dioxide, 24 mEq. per liter.

Serum electrolytes on the eighteenth hospital day were: sodium, 120 mEq., potassium 4.6 mEq., chlorides 91 mEq., and carbon dioxide 24.2 mEq. per liter.

DR. ROBERT J. HAGGERTY.* The first problem presented is the etiology of the white specks on the lips at 2 weeks of age. If they were on the outer surface of the lips, they were probably not due to Candida since this organism requires moisture and warmth to grow. Herpes simplex certainly can leave white ulcers after the vesicles have ruptured. It occurs on the lips, but not at this age. We have heard a great deal about primary infection with herpes simplex in newborn infants in recent years, but almost always this is a generalized systemic disease rather than the ulcerative stomatitis type, which is more characteristic of the child from 10 months to 2 or 3 years of age. A few instances of primary herpetic infection in which the skin vesicles were characteristic findings have been reported, but they were present all over the body and were not limited to the lips. There are, thus, points against both these diagnoses from the descriptions which are available. The child got better, only to develop croup and pneumonia. Croup is not a common disease at 3 weeks of age. I assume, from this diagnosis, that there was an inspiratory stridor which could reflect spread of the infection down to the larynx, with ulceration

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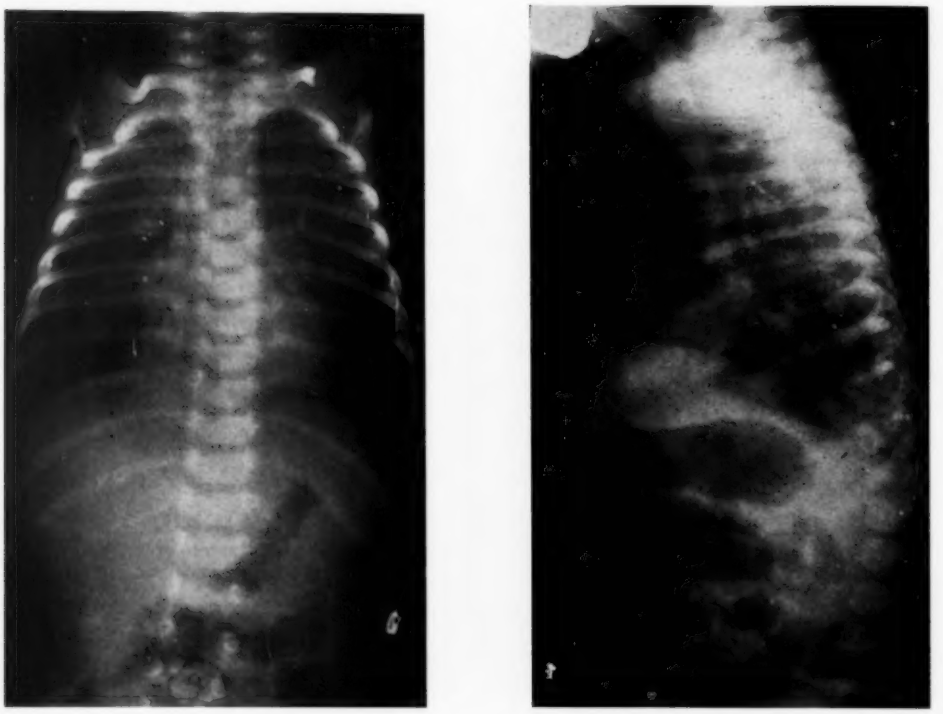

A *B*

Fig. 1. X-rays about 1 week before death. The lungs have a large volume and show streaky nodular densities extending out from the hilar area.

or edema. The etiology of this croup infection could have been the same agent which was responsible for the initial "white specks" on the lips—either a virus or bacterial agent. *Staph. aureus,* cultured from the throat, helps very little in the diagnosis of the pneumonia which followed when we recall that 70 per cent of newborn infants are colonized with Staphylococcus in the nose and throat by 72 hours of age. Isolation of an agent like this from the throat does not clearly tell us that the organism is causing pulmonary or laryngeal disease.

Dr. Alexander pointed out, some years ago, that identification of bacterial causes of lower respiratory tract disease can best be accomplished by a nasopharyngeal swab after coughing, or one can put down a small soft rubber catheter to obtain tracheal secretions for a culture. In addition, there has been renewed interest in needle puncture of the lung to obtain the etiologic agent in lobar or lobular consolidation. While it seems to be a very safe and good method, I think this technique has never been tested against the tracheal aspiration which, in my mind, is preferable. In this particular case there was no lobar or lobular infiltration. Therefore, the negative culture obtained on needle puncture of the lung later does not clearly prove that there was no bacterial agent in the lung since the needle could have missed the area of infection. After the croup and pneumonitis, ulcers on the lips and gums reappeared, associated with generalized rash and lethargy. Certainly, at this point, it would have been nice to have a stained smear of these lesions to determine if there were intranuclear inclusion bodies which would have made the diagnosis of herpes simplex more likely.

At some time during the 4 week period of

antibiotic treatment, the Pseudomonas organism appeared and persisted throughout the rest of the child's life. This infection may have been related to the antibiotics, or to contamination from such environmental objects as a mist bottle. Somewhere in this child's environment there must have been easy access to Pseudomonas organism and when this is present and host factors of resistance are sufficiently altered, this organism easily takes over. Dr. Finland has pointed out very nicely in adults that it is not the Staphylococcus that is the biggest problem in debilitated patients, but rather the gram-negative rods, particularly Pseudomonas and Proteus, and these do infect people whose host resistance is altered by many factors, including antibiotics.

With transfer to this hospital we have the problem of explaining the extraordinary failure to thrive, and the cyanosis. The cyanosis could have been respiratory in origin, although shock, or central nervous system origin, cannot be ruled out from these data. He fed poorly and was lethargic, but we have no history of vomiting. Certainly, the picture from this time until death was a classical one for Pseudomonas spreading throughout the body. These excoriated lesions are certainly like the classic skin lesions that you see with Pseudomonas, called ecthyma gangrenosum, probably resulting from a particular proteolytic toxin elaborated by this organism, which produces a severe coagulative necrosis. The blisters that occur first, and then leave a shallow punched-out necrosis-like lesion can usually be diagnosed clinically as Pseudomonas infection. These lesions are among the few which are sufficiently characteristic to allow a reliable etiological diagnosis by gross appearance. Infection then spread to the eye, producing characteristic green exudate and corneal opacity.

One other case of ocular infection with

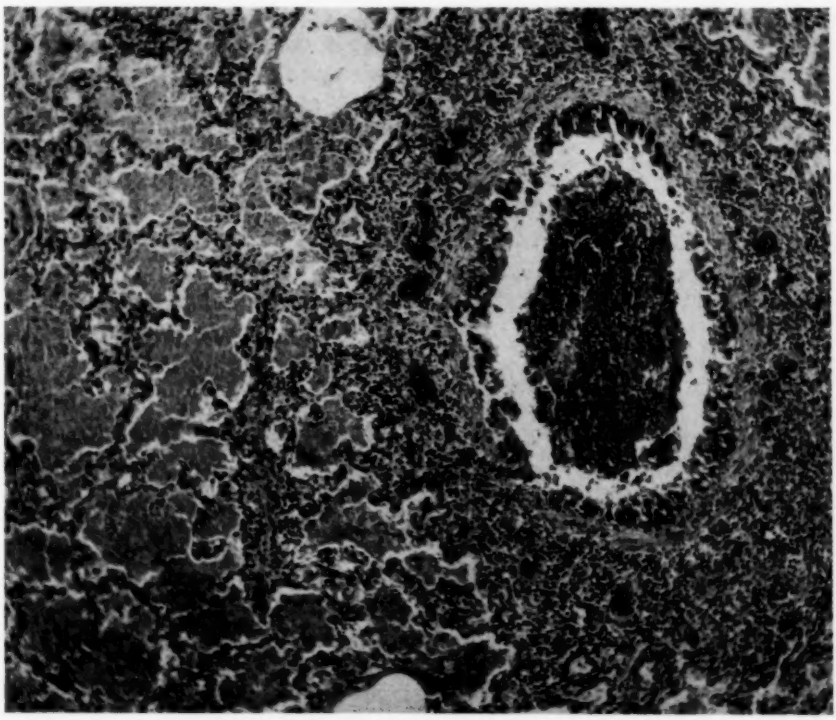

Fig. 2. The bronchus is filled with exudate and surrounded by a cellular infiltration. Most of the alveolar spaces are filled by a pink and heavy deposit. (Hematoxylin and eosin. ×170.)

Pseudomonas seen here last year was cured only by the cauterization of the cornea with a hot needle, and I think that relying only on Neo-Cortef ointment was wishful thinking.

Dr. E. B. D. Neuhauser. Films taken before admission here show a slowly progressive increase in bronchovascular markings, especially in the right lower lobe area. On films taken here, the process seems to be more diffuse, and is predominantly reticular, rather than densely consolidated. This process ultimately becomes quite severe and generalized (Fig. 1).

Dr. Haggerty. Do you associate this picture either positively or negatively with such etiological agents as Pseudomonas? In other words, would this picture rule out Pseudomonas infection of the lung?

Dr. Neuhauser. I do not think this pattern is diagnostic of any specific process, but it certainly would be compatible with Pseudomonas infection. However, it appears to be more interstitial and peribronchial than intra-alveolar in nature.

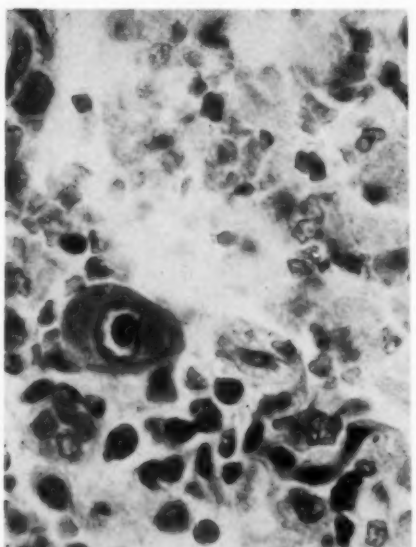

Fig. 3. Cytomegallic inclusion cell on pulmonary alveolar septum. Note the cytoplasmic mass. (Hematoxylin and eosin. ×650.)

Dr. Haggerty. This, then, is a progressive peribronchial inflammatory process in the lung and is not necessarily, or even likely to be, primarily bacterial in origin.

Now we come to a final intriguing question of the hyponatremia, hyperkalemia, and hypochloremia without any acidosis. Of course, the first thing that comes to mind is adrenal insufficiency. The child received replacement doses of adrenal steroids, not anti-inflammatory doses of steroids.

Since this child was a male, one cannot rule out by physical examination adrenal hyperplasia as the cause of an apparent adrenal insufficiency, but the lack of vomiting is against this diagnosis.

One must also consider that there may have been some sort of destructive process in the adrenal glands, as part of a generalized sepsis, but we have no clear evidence of it. Hyponatremia and hypochloremia continued and only corticosteroid treatment is mentioned. One suspects that the child received additional salt therapy, and perhaps a salt-retaining hormone as well.

There are two other disease processes that could possibly cause this general electrolyte picture—some sort of renal disease, or some sort of cerebral lesion associated with sodium loss. The absence of acidosis and of marked azotemia tends to rule against the renal mechanism despite the hematuria and proteinuria.

The most likely central nervous system disease here is an infection. Here, again, we have an interesting lack of data. The condition of any child who is this sick, lethargic, and not doing well warrants a lumbar puncture to exclude meningitis. On the basis of data given, an intracranial lesion associated with sodium loss remains a possibility. Perhaps the strongest evidence against the cerebral and renal mechanism is that the hyperkalemia apparently responded promptly. If this were adrenal insufficiency, the most likely pathogenesis would be some complication of the infection believed to be present.

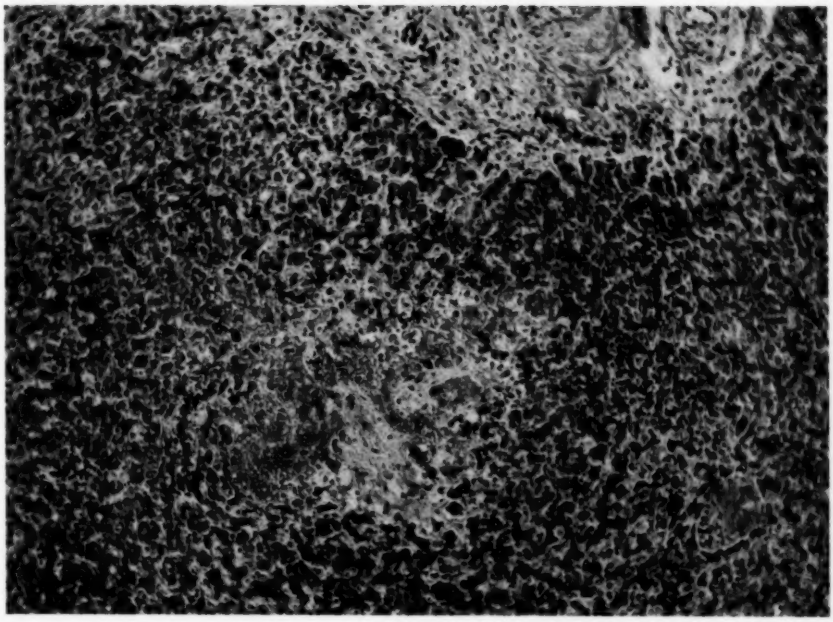

Fig. 4. Bland necrosis involves small areas of liver. Few cytomegallic inclusions were seen here. (Hematoxylin and eosin. ×150.)

In summary, I believe this patient started with some viral infection, developed a secondary bacterial infection with Pseudomonas and, finally, developed adrenal insufficiency or a central nervous system salt-wasting syndrome.

DR. HUBERT JOCKIN. At 3 months of age, this child still weighed only 6 pounds, and was markedly undernourished and underdeveloped. Both eyes had milky exudate covering the corneas, which were completely opaque. The left cornea had perforated and the right cornea perforated during the removal of the eye. Microscopically, there were keratitis and uveitis, but no chorioretinitis. There was purulent discharge from the nose and the mucous membranes of the mouth were covered with a thin film of exudate. The skin no longer showed the ecthyma as it is described. The lesions were now only slightly umbilicated and had a greenish color, as one would expect in Pseudomonas infection. When loose, desquamating skin was wiped off, multiple excoriated lesions

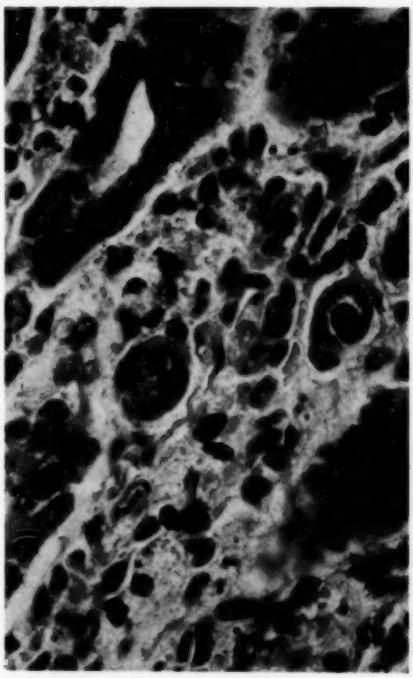

Fig. 5. Heavy involvement of gastric mucosa suggests the possibility of intravital aspiration and diagnosis. (Hematoxylin and eosin. ×650.)

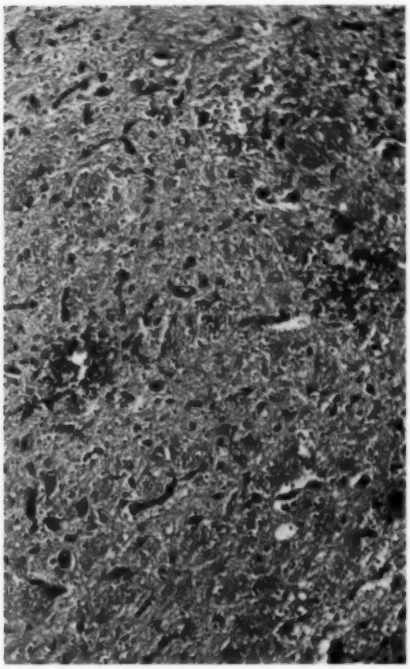

Fig. 6. Nodular glial proliferation involves brain stem. (Hematoxylin and eosin. ×125.)

appeared, but also some new skin was forming. The cultures which we took from the skin and the eye grew Pseudomonas.

The skin of the diaper area and of the scrotum was extensively involved. The lungs were markedly voluminous. They were very pale and thin and weighed about twice the normal amount. Multiple purple areas covered the surface and extended into the parenchyma. The heart appeared rather small, and indeed weighed only 15 grams, while the normal would be about 23 grams.

Microscopically (Fig. 2) one can see that in the lung there was very little air. The alveolar ducts and almost all of the alveoli were filled with pink proteinaceous material. Sometimes a bronchus was completely plugged with a cellular exudate, consisting mostly of mononuclear cells and very few polymorphonuclear cells. There was peribronchial infiltration with lymphocytes and large mononuclear cells. Probably these lesions were largely caused by the Pseudomonas.

The aveolar lining cells were enlarged and had assumed a cuboidal shape. Occasionally these cells contained large pink to purple intranuclear inclusions, sometimes associated with marginal accessory nuclear bodies or with cytoplasmic inclusions, findings which are typical of cytomegallic inclusion viruses. Some cells were multinucleate. The pulmonary septa were thick and there was infiltration by mononuclear cells.

There were bland necroses in the liver (Fig. 4) and in the pancreas. Those of the liver were small and scattered and rarely contained cytomegallic inclusion–containing cells. No inclusions were seen in the large area of pancreatic necrosis. Cytomegallic inclusion cells were seen within mucosal cells or in underlying submucosal mononuclear cells in the focally ulcerated gingival margin, in the gastric mucosa (Fig. 5), beneath the bladder mucosa, and extensive parasitization without necrosis involved the cells of the adrenal cortex. No cytomegallic inclusions were found in the somewhat underweight brain, nor were calcifications found microscopically or radiologically. However, there were multiple areas of glial proliferation in the brain stem (Fig. 6) and along the floor of the fourth ventricle, as well as in the olivary and red nuclei. Remarkably enough, the kidneys contained no cytomegallic lesions. Dr. Weller has grown a cytomegallic inclusion agent from viral cultures of lung and liver in this case; no other viruses were recovered from these tissues.

This child presents a somewhat different picture from what we usually know as *generalized cytomegallic inclusion disease of the newborn,* with its icterus, large liver, large spleen, and petechiae, frequent and early death, but it has been recognized that somewhat older children, such as this one, may present a primary interstitial pneumonia.[1] One case in the literature also reported a maculopapular rash in the early phases of the disease, just as in this child. The ocular, and possibly pulmonary, lesions were clearly caused by Pseudomonas infection, a process

which very often shows just as little polymorphonuclear response as was found in this patient. The extensive involvement of the adrenal gland provides a very attractive possible explanation for some of the biochemical and clinical aspects of this case.

DR. VAWTER. One might regard this case as transitional between the infantile generalized cytomegallic inclusion disease and that of the adult which more often involves the reticuloendothelial system to a greater extent. There are similarities here, on grounds of distribution and cytology of the hepatoadrenal necrosis of infancy ascribed, on morphologic grounds, to herpetic infection by Dr. George M. Hass.[2] However, the course here differs from that in his patients, but raises again the question of *relationship between herpes virus and cytomegalic inclusion virus*. Finally, these questions emphasize the need for virologic and immunologic characterization of many of the viruses one finds morphologically, since it seems quite clear, for instance, that isolates of cytomegallic inclusion virus vary among themselves.

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COMMENTS ON CURRENT LITERATURE

Complications of viral hepatitis

THE possible occurrence of "autoimmune" reactions against human tissue antigens in certain acute and chronic diseases has attracted increasing attention in recent years.[1, 2] In 1956, Bearn, Kunkel, and Slater[3] described a condition accompanying or associated with chronic hepatic disease. The syndrome occurred predominantly in young girls and was characterized clinically by amenorrhea, obesity, striae, arthralgia, skin rashes, with obscure febrile episodes, and evidence of moderate or severe liver damage. Most of the patients showed a marked elevation in serum gamma globulin. Biopsy specimens obtained early in the course of the disease revealed infiltration of the periportal areas with an inflammatory cell exudate made up largely of plasma cells. In a few of these cases the condition was thought to be the result of anicteric viral hepatitis, but in most instances the etiology was considered unknown. Kunkel and his associates[3] stressed the insidious onset of the disease and the absence of a history of acute infectious hepatitis.

Subsequently Page and Good[4] described the clinical management, including steroid therapy, of a number of patients, both boys and girls, showing this syndrome. They referred to the condition as a "plasma-cell hepatitis," emphasizing the presence of the plasma cell infiltrate in the liver, and called special attention to the related hypergammaglobulinemia. In their experience a history of preceding infectious hepatitis was common. Two of their patients had "definite histories of an acute attack of viral hepatitis shortly preceding their chronic illness. Three other patients had episodes of gastrointestinal distress that could conceivably represent infection with the hepatitis virus."[4] Only 5 of the 10 cases reported in this series had an insidious onset. The authors felt at the time that these 5 patients could represent cases of nonicteric, undiagnosed hepatitis. The incidence of anicteric hepatitis in young children is thought to be considerable.[5] Evidence of generalized vascular disease in their patients, along with the plasmacytosis and markedly elevated gamma globulin levels, led Page and Good to "consider the possibility that this disease is an expression of hypersensitivity." The concept of liver damage on an autoimmune basis is not a new one, and the possible sensitivity reactions include that of response to "an exogenous antigen persisting in the liver and the sensitivity of the patient to his own liver tissue."[4] As early as 1944, Eaton and his colleagues[1] were able to identify a complement-fixing antibody against human liver in the serum of patients with acute hepatitis and suggested that an autoimmune mechanism might account in some instances for late reactions to infectious hepatitis. More recently, Gajdusek[2] showed the presence of a complement-fixing antibody

against desoxyribose-nucleoprotein in patients with chronic hepatitis, lupus erythematosus, and acute glomerulonephritis. Similarly Mackay and his co-workers[6] had found 6 patients with chronic hepatitis all of whom had elevated gamma globulin levels and sedimentation rates. Mackay[6] offered the explanation that these patients represented cases of autoimmune hepatitis resulting from changed antigenicity of liver cells by viral or nutritional injury.

Six of the 10 patients observed by Page and Good[4] were considered representative of the plasma cell hepatitis syndrome: "extreme hypergammaglobulinemia, severe chronic hepatitis, and manifestations of generalized vascular disease such as skin rash, arthritis; and characterized histologically by extensive plasma cell infiltration of the liver."[4] In these 6 patients cortisone therapy was effective in suppressing all the clinical manifestations of the disease and most of the laboratory indications. In addition, improvement in the histologic appearance of the liver was evidenced by biopsy before and during therapy. In some patients, however, serious side effects of steroid therapy occurred. Four patients with chronic hepatitis, moderate hypergammaglobulinemia, and manifestations similar to those of plasma cell hepatitis also received cortisone therapy. In this group, however, the results were not encouraging. In a discussion of the plasma cell hepatitis syndrome, Page and Good point out that each of the etiological concepts offered in recent years is logical and tenable: autoimmune disease of the liver, hepatic damage occurring during the course of acute virus hepatitis, possibly as a result of hypersensitivity to the virus; liver damage in chronic hepatitis; and postnecrotic cirrhosis following virus hepatitis resulting from the actual persistence of virus in the tissue. In the latter hypothesis the plasmacytosis and elevated gamma globulin levels could be regarded as the result of prolonged antigenic stimulation by the virus.

A recent publication by these authors is of special interest. This report[7] deals with fatal complications of virus hepatitis in 2 patients with agammaglobulinemia. Severe cirrhosis and subacute yellow atrophy of the liver occurred in 2 patients with agammaglobulinemia. In both of these patients, one with acquired agammaglobulinemia and one with the inherited sex-linked form of the disease, the levels of gamma globulin were so low that the immunologic responsiveness was almost completely absent. The adult patient studied, a male, had experienced recurrent pneumonia following a chest operation for the removal of an anterior mediastinal mass. Recurrent pneumonia began 6 months following thoracotomy. A diagnosis of agammaglobulinemia was established by electrophoretic study of the patient's serum. Further studies indicated that the patient was unable to form antibodies to bacterial and viral antigens following antigenic stimulation. In addition to the pulmonary difficulties, this patient had a history of arthritis of the wrists, elbows, knees, and shoulders. Prior to the administration of any gamma globulin for prophylaxis against infection, the patient had suffered from anorexia and a mild epigastric distress, followed in two weeks by the insidious onset of jaundice. The arthritis which had been moderately severe disappeared completely after the onset of jaundice. Physical examination at this time revealed marked icterus and a palpable nontender liver.

Laboratory studies showed bilirubinuria and hyperbilirubinemia. A tentative diagnosis of serum hepatitis was made and a therapeutic regimen of gamma globulin, oral vitamin K, and oral neomycin was initiated. Despite all efforts at therapy including the use of steroids, the course of the disease was rapidly progressive and the patient died in hepatic coma three days after admission to the hospital. Postmortem examination showed changes consistent with the diagnosis of acute viral hepatitis progressing to subacute yellow atrophy or massive necrosis of the liver. Pancreatitis which was present also may have contributed to the patient's death; however, the pathologic changes in the liver were considered sufficient to account for the fatal outcome.

The second case described is that of a white male child who had been observed closely from birth because his older brother was known to have agammaglobulinemia. Normal gamma globulin level failed to develop in this child also, and a diagnosis of agammaglobulinemia was established by the time that he was 6 months of age. Gamma globulin prophylaxis was initiated at the age of 19 months, 20 c.c. of gamma globulin being given intramuscularly every 30 days until the age of 3½ years when the monthly amount was increased to 40 c.c. intramuscularly. During the 6 months prior to his admission to the hospital these intramuscular injections of gamma globulin were the only injections received. At the age of 4 years this boy was admitted to the hospital because of jaundice which had followed an episode of anorexia and vomiting of 5 days' duration. On physical examination the liver was firm, nontender, and palpable 6 centimeters below the right costal margin. Laboratory studies at this time revealed bilirubin, 4.7 mg. per cent direct, and 8.5 mg. per cent total; Bromsulfalein retention, 25 per cent in 45 minutes; thymol turbidity, 2 units; the cephalin-cholesterol flocculation test, negative; and prothrombin time, 18.3 seconds with control of 13.4 seconds. A tentative diagnosis of serum hepatitis was made and therapy consisting of gamma globulin, oral neomycin, and vitamin K was initiated. The child improved and was discharged from the hospital after a stay of 5 weeks.

Six weeks later, because of the recurrence of symptoms, anorexia and vomiting, with more severe jaundice, the patient was readmitted. Physical examination revealed jaundice, a distended abdomen with a palpable fluid wave, and liver palpable 5 centimeters below the right costal margin. Laboratory findings included serum bilirubin, 3.6 mg. per cent direct, and 7.5 mg. per cent total; thymol turbidity, 1 unit; reaction to the cephalin-cholesterol flocculation test, trace; and prothrombin time, 22.8 seconds with a control of 13.6 seconds. Because the patient's condition was deteriorating rapidly steroid therapy was initiated, 180 mg. (300 mg. per square meter per 24 hours) of cortisone daily, 50 mg. of neomycin three times daily, 5 mg. vitamin K twice daily, and 30 c.c. gamma globulin weekly. Cortisone therapy was discontinued after 24 days because of hypertension, and therapy with triamcinolone, 24 mg. daily, was started. This patient experienced a stormy recurrent course over a period of about one year. At the final admission the illness was rapidly fatal and the child died in hepatic coma.

Autopsy studies revealed ascites and an enlarged finely nodular liver. Microscopic examination showed the same pathologic condition noted earlier in a liver biopsy: distortion of the normal lobular pattern by fibrosis, many areas of nodular regeneration of parenchymal cells, marked infiltration of periportal round cells, with adjacent parenchymal cells showing degenerative changes. Intranuclear inclusion bodies were noted frequently, but no cytoplasmic inclusion bodies were observed. The inflammatory cell infiltrate in this case was completely lacking in plasma cells, an observation which the authors emphasize as very unusual in postnecrotic cirrhosis. They consider that the case represents serum hepatitis progressing to postnecrotic cirrhosis in a child with congenital agammaglobulinemia. Both of these patients with fatal hepatitis are thought to have had adequate opportunity to acquire hepatic virus B. The inability of these patients with agammaglobulinemia to combat the hepatitis virus is considered somewhat surprising, since many of the patients with this defect do cope with virus disease in a reasonably satisfactory manner. From a study of these two fatal cases of virus hepatitis and of several other patients who recovered, the authors are inclined to believe that "the plasmacytosis of liver and bone marrow and the hypergammaglobulinemia, usually observed in patients with postnecrotic cirrhosis and chronic hepatic disease, are secondary phenomena (perhaps a function of the prolonged presence of virus which cannot be eliminated) rather than important pathogenetic indications."[7] They express the

belief that the "overwhelming destruction of hepatic parenchyma in acute and subacute atrophy of the liver following virus hepatitis may be more directly attributable to the action of the virus itself"[7] than to the formation of autoantibodies, especially in the patients with agammaglobulinemia.

The two concepts discussed by these authors are of great importance and are currently under study in a number of centers: (1) the potential autoimmune mechanisms and the response of the body to its own damaged or altered tissues; and (2) the possible persistence of viruses in the tissues, their role in the pathogenesis of disease, and their influence on the immunity status of the body.

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Books

Insulin.

F. G. Young, editor, British Medical Bulletin, Volume 16, Number 3, London, England, 1960, 84 pages. Price $3.25.

Professor F. G. Young quite aptly states in the introduction of this excellent symposium concerning insulin that "we can be sure that the elusiveness, importance, and subtlety of action of insulin will continue to attract investigations on all aspects of this hormone and its effects for many years to come." This number of the *British Medical Bulletin* consists of 16 papers contributed by 19 leading British investigators.

The first paper "Forty Years of Interest in Insulin" by C. H. Best gives a detailed account of the early work with insulin by the Toronto group and will unquestionably be of great interest to medical historians as well as to all physicians who have ever used insulin, "the most economically important of all purified proteins." The second paper on the chemistry of insulin by F. Sanger is largely based on his Nobel Prize Lecture in 1958. The techniques introduced by Sanger have been vigorously applied to study of the structure of other proteins, especially those of the pituitary, and these are ably reviewed by Ieuan Harris in a paper entitled "The Chemistry of Pituitary Polypeptide Hormones."

Other papers deal with methods of insulin assay, insulin in blood, insulin antagonists, insulin antibodies, and mechanism of action of insulin. The action of insulin on carbohydrate, protein, and fatty acid metabolism is summarized in 3 papers and several contributions on the insulin substitutes are also included.

This issue of the *British Medical Bulletin* is at the usual high level of standards of these symposia. It is concise but well written, and manages to summarize, as well as to interpret, a large body of information concerning the subject at hand.

ANGELO M. DI GEORGE, M.D.

The metabolic basis of inherited disease.

J. B. Stanbury, J. B. Wyngaarden, and D. S. Fredrickson, editors, New York, 1960, McGraw-Hill Book Company, Inc., 1,477 Pages. Price $30.00.

This is the most recent of a variety of books on this same general theme which have been published during the past year. It differs from the other books on the subject in that this is undoubtedly the most comprehensive work on heritable disorders of metabolism to appear thus far. As indicated in the Preface, only those disorders have been included "for which an appreciable body of knowledge now exists." The heritable disorders of connective tissue have not been included because they were "recently well reviewed by Victor A. McKusick."

The three editors have "enlisted the collaboration of investigators actively engaged in the intensive study of specific heritable disorders." The 46 contributors have been selected because of their interest in, contributions to, and eminence in, the particular subject about which they write.

The book is divided into 11 parts: (1) Introduction, 2) Diseases Manifest Primarily as Disorders of Carbohydrate Metabolism, (3) Diseases Primarily Related to Disorders of Amino Acid Metabolism, (4) Diseases Characterized by Evidence of Abnormal Lipid Metabolism, (5) Disorders of Steroid Metabolism, (6) Diseases of Purine and Pyrimidine Metabolism, (7) Diseases Primarily Manifest as Abnormalities in Metal Metabolism, (8) Diseases of Porphyrin Metabolism, (9 Diseases Manifest Primarily in the Blood and Blood Forming Tissues, (10) Diseases Manifest Primarily in Renal Tubular Transport, and (11) Diseases Involving a Deficiency of Circulating Enzymes or Plasma Proteins. Each part consists of from 1 to 8 chapters and each chapter, dealing with a disease entity, begins with a historical review of its discovery or characterization. The biochemical defect is

thoroughly discussed and sufficient background of biochemical and physiologic information is included to provide a thorough understanding of the disordered metabolism. Descriptions of clinical manifestations include all the nuances and are usually correlated with the biochemical aberration. The genetic aspects of each disorder are discussed and illustrated with pedigrees. The bibliography at the end of each chapter includes virtually every paper related to the subject at hand and may number up to 300 references. These references are up to date and include most of the pertinent foreign papers.

The subject matter of this book consists primarily of rare disorders, in fact, 3 chapters (38 pages) deal with disorders that have been described only once—xanthinuria, oroticaciduria, and glycinuria. Furthermore, most of the disorders described have been reported or biochemically characterized for the first time within the past 10 years. Seventy-five to 100 per cent (depending on the chapter) of the information in this text has been garnered only in the past 10 years. One wonders if this opus will grow to 2 or 3 volumes in the next 10 years.

The text is highly readable and the relative uniformity of style, charts, diagrams, pedigrees, and metabolic maps in the various sections indicates an excellent job of editing and helps to make this a *book* rather than a collection of papers by different authors.

This will be an invaluable reference source to all physicians. With the possible exception of two disorders, gout and hemochromatosis, all of the entities are in the domain of the pediatrician. No pediatric department should be without a copy. Many individuals who would desire this book for their private libraries will be discouraged by the price; it is rather overpriced when compared to other collaborative texts of similar size and quality.

ANGELO M. DI GEORGE, M.D.

The thyroid gland.

N. B. Myant, editor, British Medical Bulletin, Volume 16, Number 2. London, England, 1960, 80 pages. Price $3.25.

This number of the *British Medical Bulletin* is devoted to a symposium on recent advances in various aspects of knowledge concerning the thyroid gland. As Sir Charles Harington states in his introduction, "the long history of work on the thyroid gland . . . contains many illustrations of the peculiar fascination that research on this subject has exercised on scientific workers who have been drawn into it from many different disciplines."

Twenty leading British authorities in a variety of disciplines have contributed 15 papers in which they describe research engaged in by themselves. Each chapter is an authoritative, compact, lucid review of current concepts in the specific aspect of thyroidology under consideration. Chapters of special interest to pediatricians include, The Association of Deafness With Thyroid Dysfunction by W. R. Trotter, Sporadic Goitrous Cretinism by E. M. McGirr, Influence of the Thyroid on the Central Nervous System by J. T. Eayrs, and The Passage of Thyroid Hormone From Mother to Foetus and Its Relation to Foetal Development by C. Osorio and N. B. Myant. This is highly recommended to those with a special interest in the thyroid gland.

ANGELO M. DI GEORGE, M.D.

News and notes

The Cook County Graduate School of Medicine offers an intensive course in **Neuromuscular Diseases of Children,** with emphasis on **Cerebral Palsy,** to be given by Dr. Meyer A. Perlstein, June 12 to June 23, 1961. Emphasis will be on practical clinical aspects of treatment and rehabilitation. The fee is $285; application should be made, as early as possible, to John W. Neal, Registrar, 707 S. Wood Street, Chicago, Ill.

The annual clinical meeting of the **Intermountain Pediatric Society** will take place at the Challenger Inn, Sun Valley, Idaho, June 19 to 21. Speakers include Dr. Robert Good, Dr. Benjamin H. Landing, Dr. Waldo E. Nelson, Dr. William A. Silverman, and Dr. Alex J. Steigman. The meeting is open to all physicians.

The **Thirteenth Annual Summer Clinics** of the Denver Children's Hospital are to be held June 21, 22, and 23, 1961. The four guest speakers are: Dr. Amos Christie, of Vanderbilt University; Dr. Edward B. Neuhauser, of The Children's Medical Center, Boston; Dr. Thomas V. Santulli, of Columbia-Presbyterian Medical Center, New York; and Dr. Wolf W. Zuelzer, of The Children's Hospital of Michigan, in Detroit. For further information write the Director of Medical Education, Denver Children's Hospital, Denver, Colo.

The increasing interest of potential candidates in the field of pediatric neurology challenges the two American Boards most concerned to determine guide lines for program directors in pediatrics and in neurology and for potential candidates in these disciplines. The **Committees on Child Neurology of the American Board of Pediatrics and the American Board of Psychiatry and Neurology** met on Sept. 21, 1959, and Oct. 21, 1960, and submitted to their respective Boards the following statement:

Recommendations for a desirable training program in pediatric neurology:

1. A year of approved internship.

2. Approved residency training in a pediatric service, sufficient to meet established requirements of the American Board of Pediatrics.

3. Two years of residency training in general neurology, including the basic neurological sciences, and under conditions consistent with established requirements of the American Board of Psychiatry and Neurology.

4. A year of residency training in a pediatric neurology service meeting the established requirements of the American Board of Psychiatry and Neurology.

Flexibility should be allowed in the order in which these components of the training program are taken.

Training program facilities.

1. The pediatric neurology service should be in the setting of an active pediatric service with a sufficient number of beds for the number of residents in training and an active outpatient department. It is also recommended that there be opportunities for the trainee to study the newborn, and that he also have opportunity to maintain continuing contact with patients in this category.

2. The pediatric neurology service should be under qualified neurological direction.

3. Patient beds assigned to the pediatric neurology service should preferably be in close physical contact with the pediatric service and under independent pediatric neurological direction.

4. The pediatric neurology resident should have responsibility under competent supervision for patient care.

5. It it also desirable that the pediatric neurology program be in a setting in which basic neurological science contacts are readily available.

The adoption of these recommendations

might serve as a preliminary step toward further consideration of a formalized subspecialty board in pediatric neurology.

John McK. Mitchell, M.D.
Executive Secretary
American Board of Pediatrics, Inc.

David A. Boyd, Jr., M.D.
Executive Secretary-Treasurer
American Board of Psychiatry and Neurology, Inc.

A **Symposium on Pediatric Surgery** will be held at New York University Medical Center, New York City, from May 4 through 6, 1961. Latest methods and techniques of diagnosis and surgical management will be stressed, and surgeons, pediatricians, and general practitioners are invited to attend. Tuition is $75; address inquiries to Office of the Associate Dean, New York University Post-Graduate Medical School, 550 First Avenue, New York 16, N. Y.

A **Postgraduate Course in Pediatrics** will be given at Massachusetts General Hospital by the Department of Pediatrics of Harvard Medical School, June 5 to 16, 1961, 9:15 A.M. to 4:30 P.M., daily. The first 7 days concentrate on medical, neurological, surgical, orthopedic, cardiac, allergic, dermatologic, psychiatric, eye, ear, and x-ray problems. The last 4 days, June 13 to 16, are devoted to a course in **Pediatric Metabolism and Endocrinology** which may be taken separately. For further information write Courses for Graduates, Harvard Medical School, 25 Shattuck Street, Boston, Mass.

The annual meeting of the **Kentucky Pediatric Society,** to be held at 2 P.M., April 20, 1961, at the Brown Hotel, Louisville, will be addressed by Dr. Robert Ward of Los Angeles on the subject of "New Developments in Viral Hepatitis," and by Dr. Samuel Kaplan of Cincinnati, on "Bedside Diagnosis of Heart Disease in Children."

On May 8, 1961, the medical staff of Childrens Memorial Hospital, Omaha, Nebraska, will sponsor a seminar on **Pediatric Cardiology.** Principal speakers will be Dr. C. Walton Lillehei and Dr. James W. DuShane, both of the University of Minnesota. For information write to Postgraduate Seminar, Children's Memorial Hospital, Omaha 5, Nebraska.

EDITOR'S COLUMN

A pediatric ethical question

"ETHICS" are at times perplexing. The clear-cut concepts of "right and wrong," "good and bad" of early childhood fall by the wayside and become hazy as an individual grows and develops and finds they must be modified by many factors: time and place, religious beliefs, teaching, nationality, racial customs, traditions, social and economic levels, and man-made law which may change from decade to decade, among others. Any one of these may raise doubts as to a specific act being categorically considered "good or bad," "right or wrong." Finally, many of us reach the conclusion arrived at by the great philosopher Immanuel Kant, nearly 200 years ago, that nothing can be considered unqualifiedly good but a good intention. Then that old saying comes to mind, "Hell is paved with good intentions." It is certainly confusing at times when it comes to deciding on the "moral" justification of a specific act.

This is especially true of medical ethics, as medicine has to do with human beings, their birth, life, and death. One of the present-day medical "ethical conflicts" revolves around euthanasia. Another is the "prolongation of death" by the use of recently developed techniques, such as transfusion, intravenous feeding, fluid therapy, and the cardiac pacemaker, along with the development of such drugs as the antibiotics. Whether it is morally justifiable to use these measures to prolong the life of elderly patients with incurable cancer or senility associated with severe cerebral or cardiac lesions is a debatable question. Personally, we dislike the movement to legalize euthanasia for the simple reason that it would place an almost unbearable decision on the physician. But the problems associated with the "prolongation of death" are with us and we cannot avoid them. A most interesting discussion of the subject by Professor Joseph Fletcher of the Episcopal Theological School in Cambridge, Massachusetts, was recently published in the October, 1960, issue of *Harper's Magazine*. It was published as part of a symposium on current medical trends and problems which is excellent and deserves a wide reading by physicians. One should not be deceived by the title, "The Crisis in American Medicine." In some way—for eye-catching purposes, perhaps—the usually well-edited *Harper's* made a semantic error. Pratically none of these well-written articles can be associated with the word "crisis," even in the highest flights of the imagination.

Although most of the current discussions of ethical problems are concerned with geriatrics, pediatrics also has some serious ethical questions. One of these has to do with Mongolian idiocy, which accounts for roughly one fourth of the cases of mental retardation. It is incurable and unimprovable, and only within the last two years has light been thrown on the causative mechanism. In earlier years the physician faced

with this condition had one source of comfort, even though it was bleak, for a condition he knew he could not help in any way. Nature had somehow provided to the Mongol a compensating abnormality in the form of a low resistance to infection. Few patients with Mongolism lived beyond infancy or early childhood. But today, with the use of modern techniques and the newer drugs, the life of the Mongol can often be saved, and he continues a vegetative existence, worthless to himself and a burden to his family and to society. Is the use of these "miracles of modern medical science" morally justified for patients with Mongolian idiocy? Is interference with the processes of nature justified in this condition?

Then, to add to the problem, in the last few years came the brilliant development of cardiac surgery. Congenital cardiac lesions are a part of the picture of Mongolian idiocy. Should we or should we not advise operation for a child who has Mongolism with a cardiac lesion?

We have discussed this "ethical problem" brought on by the developments of medical science in recent years with a number of pediatricians. It is a perplexing problem. As might be expected, opinion is divided. There is one group with a decided "yes" answer and another with a decided "no." A third group believes in selective judgment. What has been most interesting has been the background, training, and interest of the men in each category. Department heads who have reached their position through research and scientific interests and whose relationship to patients has been confined to the hospital, make up, to a large extent, the "pro" group, whereas those whose interests are rather in the humanitarian side of medicine, and who have had to face the devastating influence of a Mongolian idiot on family life, on normal siblings, and on marital relationships, chiefly comprise the "con" group. We have asked some of the "selective" group if they ever thought of their attitude as one of "playing God." It is not a question that can be decided by a majority vote, as ethical problems are matters that everyone has to decide for himself. The decision will depend on the individual's background and interests, to a large extent. We are not taking sides editorially or propagandizing for a personally held viewpoint. Our purpose is rather to point out that the pediatrician faces important problems and decisions in medicine that cannot be solved by medical science and research.

My personal viewpoint, reached gradually as years of practice and experience lengthened, places me squarely in the "con" group. However, I am not critical of those who reach a different ethical viewpoint of the question discussed.

BORDEN S. VEEDER, M.D.

The legal rights of the child

A RECENT decision (Vasta versus Malaze) in the State Supreme Court of New York touched upon a matter of fundamental importance to pediatricians. A 3-year-old boy, who had been raised by foster parents since his fifth day of life, became the center of a court dispute when his natural mother sued to obtain his custody.

The facts in the case were as follows: The child was born out of wedlock to a 14-year-old girl. He was given, apparently by the maternal grandfather, to a childless couple who raised the child as their own, planning to adopt him. Three years later the natural mother who had since married sued to have the child returned to her. She claimed that her father, now deceased, had arranged for the transfer of the child against

her wishes. Testimony during the trial brought out that she had made no attempt to see the child or to seek assistance in obtaining his return until shortly before the trial. Testimony also brought out that her marriage was a stormy one, and that she was recently separated from her husband.

The attorney for the foster parents introduced psychiatric opinions during the trial which agreed that a removal from the home would be likely to have deleterious effects upon the child's future emotional development.

In his decision to leave the child with his foster parents Judge John Cone stressed the significance of the psychiatric testimony in emphasizing the adverse effects that such a separation would have upon the child. The significance of this precedent-shattering decision is that, for the first time, the law has recognized the right of the child to a proper home. Hitherto the rights of the parents to their child had been considered paramount, regardless of the deleterious effects on the child. By this decision Judge Cone declared, in effect, that under certain circumstances children have rights which transcend those of their parents.

JAMES M. TOOLAN, M.D.